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_____ A.A. Sequence
_____ Structure
_____ Bibliographic

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✓ Dialog
_____ APS
_____ Geninfo
_____ SDC
_____ DARC/Questel
_____ Other

PTO-1590 (9-90)

Devi, S.
09/622284

- key terms

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     FILE 'REGISTRY' ENTERED AT 09:27:50 ON 15 SEP 2003
                E ENTEROTOXIN B/CN 5
L1             28 S ENTEROTOXIN B ?/CN

     FILE 'HCAPLUS' ENTERED AT 09:29:10 ON 15 SEP 2003
L1             28 SEA FILE=REGISTRY ABB=ON  PLU=ON  ENTEROTOXIN B ?/CN
L2           1524 SEA FILE=HCAPLUS ABB=ON  PLU=ON  (L1 OR (ENTEROTOXIN OR
                  ENTERO TOXIN)(W)B)(S)STAPHYLOCOCC? OR SEB(S)STAPHYLOCOCC?

L3             26 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L2 AND ((IMMUNOPATH? OR
                  IMMUN? PATH? OR RA OR ARTHRIT?)(S)(TREAT? OR THERAP? OR
                  PREVENT? OR REMED?) OR ANTIARTHRIT?)
L4              2 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L3 AND (MUTAT? OR
                  MODIF? OR MUTAT? OR POLYMORPH? OR POLY MORPH?)



L1             28 SEA FILE=REGISTRY ABB=ON  PLU=ON  ENTEROTOXIN B ?/CN
L2           1524 SEA FILE=HCAPLUS ABB=ON  PLU=ON  (L1 OR (ENTEROTOXIN OR
                  ENTERO TOXIN)(W)B)(S)STAPHYLOCOCC? OR SEB(S)STAPHYLOCOCC?

L3             26 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L2 AND ((IMMUNOPATH? OR
                  IMMUN? PATH? OR RA OR ARTHRIT?)(S)(TREAT? OR THERAP? OR
                  PREVENT? OR REMED?) OR ANTIARTHRIT?)
L5             20 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L3 AND (T(W)(CELL OR
                  LYMPHOCYT?) OR TCR OR VB? OR V BETA)


L6             21 L4 OR L5

L6   ANSWER 1 OF 21  HCAPLUS  COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER:         2003:656800  HCAPLUS
TITLE:                    Immune-modulating peptide made of S. aureus
                          enterotoxin B
INVENTOR(S):              Neuber, Karsten
PATENT ASSIGNEE(S):       Agelab Pharma G.m.b.H., Germany
SOURCE:                   PCT Int. Appl., 46 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 German
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.        KIND  DATE          APPLICATION NO.  DATE
     ----------------  ----  --------      ---------------  --------
     WO 2003068812      A2   20030821      WO 2003-EP1511   20030214
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH,
             CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD,
             GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ,
             LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ,
             NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ,
             TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW,
             AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
         RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE,
             BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT,
             LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA,
             GN, GQ, GW, ML, MR, NE, SN, TD, TG
     DE 10207734        A1   20030904      DE 2002-10207734 20020215
```

PRIORITY APPLN. INFO.: DE 2002-10207734 A 20020215
DE 2002-10240866 A 20020904

AB The invention relates particularly to peptides which are specifically capable of binding IgE antibodies and can be obtained from naturally occurring S. aureus enterotoxin B (SEB), for example. The immune-modulating properties thereof are substantially different from those of bacterial SEB. Surprisingly, the inventive peptides do not induce proliferation of **T cells**, as opposed to SEB. Due to their properties, said peptides are suitable for **treating** diseases that are characterized by an increased serum IgE level and/or an increased prodn. of interferon gamma and for **treating** diseases that are characterized by an imbalance in the Th1 and Th2 cytokine response, e.g. atopic eczema, lupus erythematosus, Crohn's disease, multiple sclerosis, psoriasis, and rheumatoid **arthritis**.

L6 ANSWER 2 OF 21 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2003:656216 HCAPLUS
TITLE: Superantigen conjugates and receptors specific for lipid-based tumor-associated antigens for treatment of neoplastic disease
INVENTOR(S): Terman, David S.
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 151 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2003157113	A1	20030821	US 2000-751708	20001228

PRIORITY APPLN. INFO.: US 1999-173371P P 19991228

AB The present invention comprises compns. and methods for treating a tumor or neoplastic disease in a host. The methods employ conjugates, fusion proteins, or naked nucleic acids encoding superantigen polypeptides, and other structures that preferentially bind to tumor cells and are capable of inducing tumoricidal apoptosis. The addnl. mol. serves the following functions: (1) to target a receptor (digalactosylceramide) expressed on tumor cells in vivo and induce tumor cell apoptosis (e.g., superantigen-verotoxin conjugates); (2) to target receptors expressed on tumor sinusoidal endothelium induce apoptosis and a prothrombotic state (e.g., superantigen-oxyLDL conjugates and superantigen-Lp(a) conjugates); (3) to activate a dormant population of tumoricidal NKT cells (e.g., superantigen-digalactosylceramides, superantigens-glycosylphosphatidylinositol-digalactosylceramide complexes); (4) target receptors for integrins expressed on tumor microvasculature (e.g., superantigen-RGD conjugates); (5) naked DNA administered intratumorally inducing tumor cell expression in vivo of receptors for ligands which produce apoptosis and inflammation. Also provided are superantigen-glycolipid conjugates and vesicles that are loaded onto antigen-presenting cells to activate both **T cells** and NKT cells. Cell-based vaccines comprise tumor cells engineered to express a superantigen along with glycolipids products which, when expressed, render the cells capable of eliciting an effective anti-tumor immune response in a mammal into

which these cells are introduced. Included among these compns. are tumor cells, hybrid cells of tumor cells and accessory cells, preferably dendritic cells. Also provided are tumoricidal **T cells** and NKT cells devoid of inhibitory receptors or inhibitory signaling motifs which are hyperresponsive to the the above compns. and lipid-based tumor assocd. antigens that can be administered for adoptive immunotherapy of cancer and infectious diseases.

L6 ANSWER 3 OF 21 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2003:301104 HCAPLUS
DOCUMENT NUMBER: 138:319801
TITLE: Production and purification of recombinant **staphylococcal enterotoxin B** for vaccine preparation
INVENTOR(S): Coffman, J. Daniel; Giardina, Steven L.; Zhu, Jianwei
PATENT ASSIGNEE(S): The Government of the United States of America, as Represented by the Department of Health and Human Services, USA
SOURCE: PCT Int. Appl., 66 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003031471	A1	20030417	WO 2002-US31114	20020927

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2001-328017P P 20011009

AB The invention provides processes and compns. for fermn., recovery and purifn. of recombinant bacterial superantigens (rSAgs), exemplified by a recombinant **staphylococcal enterotoxin B SEB** protein **mutated** for use in administration to mammalian recipient. This process generates an economically viable quantity of rSEB vaccine protein meeting FDA parenteral drug specifications. The purifn. methods generally involve multiple steps including hydrophobic interaction chromatog. (HIC), buffer exchange (desalting), and cation exchange. The final product of the purifn. is a highly purified rSAg compn. satisfying clin. safety criteria and is immunogenic and protective against lethal aerosol challenge in a murine model. The methods and compns. of the invention provide useful tools for **treatment** of disease and other conditions caused by bacterial SAgs, including food poisoning, bacterial **arthritis** and other autoimmune disorders, toxic shock

syndrome, and insults attributed to the potential use of SAg biowarfare agents.

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 4 OF 21 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2000:513542 HCAPLUS
DOCUMENT NUMBER: 133:134176
TITLE: Methods for the prevention and treatment of diseases caused by an inflammatory response mediated by endogenous substance p by using anti-substance p antibodies
INVENTOR(S): Tripp, Ralph A.; Anderson, Larry J.; Moore, Deborah D.
PATENT ASSIGNEE(S): United States Dept. of Health and Human Services, USA
SOURCE: PCT Int. Appl., 45 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000043040	A1	20000727	WO 2000-US1032	20000114
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2359776	AA	20000727	CA 2000-2359776	20000114

PRIORITY APPLN. INFO.: US 1999-116835P P 19990122
WO 2000-US1032 W 20000114

AB The present invention provides methods for preventing or treating a disease in a subject which is caused by an inflammatory response to a disease or syndrome which is mediated by endogenous substance P. These methods comprise the administration to the subject of a pharmaceutically-effective amt. of anti-substance P antibodies, or anti-substance P antibody fragments, such as F(ab)2 fragments, thereby inhibiting the activity of endogenous substance P in the subject. By inhibiting the activity of endogenous substance P in the subject, the levels of cytokines produced by **T lymphocytes** present in the subject are reduced, the signals which direct the inflammatory response to the infection become altered, and the amt. of cytokine-induced inflammation becomes reduced. Respiratory syncytial virus is one example of an agent which causes an infection which often results in a disease caused by an inflammatory response to the infection mediated by endogenous substance P. Generally, from about 0.001 mg to about 10 g of anti-substance P antibodies, or anti-substance P antibody fragments, per kg of body wt. per day are administered to a mammalian subject, with from about 1 mg to about 1000 mg of anti-substance P

antibodies, or anti-substance P antibody fragments, per kg of body wt. per day being preferred.

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 5 OF 21 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2000:436193 HCAPLUS
DOCUMENT NUMBER: 133:290820
TITLE: In vitro and in vivo inhibition of activation-induced **T cell** apoptosis by bucillamine
AUTHOR(S): Okazaki, Hitoaki; Sato, Hidetomo; Kamimura, Takeshi; Hirata, Daisuke; Iwamoto, Masahiro; Yoshio, Taku; Mimori, Akio; Masuyama, Jun-Ichi; Kano, Shogo; Minota, Seiji
CORPORATE SOURCE: Division of Clinical Immunology, Jichi Medical School, Tochigi-Ken, 329-04, Japan
SOURCE: Journal of Rheumatology (2000), 27(6), 1358-1364
CODEN: JRHUA9; ISSN: 0315-162X
PUBLISHER: Journal of Rheumatology Publishing Co. Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB This work investigated the mechanism of autoimmune phenomena, occasionally seen in patients with rheumatoid **arthritis** **treated** with bucillamine (BUC) and D-penicillamine (D-Pen), by evaluating their effects on apoptosis of **T** **cells** induced by **T cell** receptor activation or by dexamethasone. In vitro apoptosis was induced in a **T-cell** hybridoma (SSP3.7) and a B-cell line (WEHI 231) by activation of their resp. receptors or by dexamethasone, in the presence or absence of BUC or D-Pen. In vivo apoptosis was induced in BALB/c mice by **staphylococcal** **enterotoxin B** (**SEB**), with or without BUC or D-Pen, and thymocytes were examd. for it. Stimulation with anti-CD3 and dexamethasone induced apoptosis in 72% and 71%, resp., of the SSP3.7 cells. However, only 16% of SSP3.7 cells became apoptotic by anti-CD3 when BUC was added to the culture media. By contrast, 80% of SSP3.7 cells became apoptotic when stimulated by dexamethasone, even in the presence of BUC. BUC did not affect apoptosis of WEHI 231 cells induced by anti-IgM. Although SA981 (a metabolite of BUC) inhibited the apoptosis of SSP3.7 cells induced by anti-CD3, D-Pen did not. BUC, SA981, or D-Pen did not influence the extent of interleukin 2 secretion stimulated by anti-CD3. In contrast, both BUC and D-Pen inhibited the apoptosis of **V.** **beta**.8+ thymocytes induced in vivo by SEB superantigen. Neither BUC nor D-Pen changed the no. of CD4+CD8+ thymocytes in BALB/c mice injected with dexamethasone. Thus, BUC decreased, while D-Pen did not, the apoptosis of **T cells** stimulated by anti-CD3 in vitro, although they both inhibited the deletion of immature thymocytes reactive with SEB in vivo. This may explain the autoimmune phenomena sometimes seen during the treatment of rheumatic patients with these drugs.

REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 6 OF 21 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 2000:84832 HCAPLUS
DOCUMENT NUMBER: 132:132335
TITLE: Treatment of autoimmune conditions with copolymer 1 and related copolymers and peptides
INVENTOR(S): Aharoni, Rina; Teitelbaum, Dvora; Arnon, Ruth; Sela, Michael; Fridkis-Hareli, Masha; Strominger, Jack L.
PATENT ASSIGNEE(S): Yeda Research and Development Co., Ltd, Israel; President and Fellows of Harvard College
SOURCE: PCT Int. Appl., 147 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000005250	A1	20000203	WO 1999-US16747	19990723
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, US, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2337688	AA	20000203	CA 1999-2337688	19990723
AU 9952262	A1	20000214	AU 1999-52262	19990723
EP 1098902	A1	20010516	EP 1999-937423	19990723
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2002521387	T2	20020716	JP 2000-561206	19990723
US 6514938	B1	20030204	US 1999-405743	19990924
NO 2001000329	A	20010308	NO 2001-329	20010119
US 2002055466	A1	20020509	US 2001-768872	20010123

PRIORITY APPLN. INFO.:

US 1998-93859P	P	19980723
US 1998-101825P	P	19980925
US 1998-102960P	P	19981002
US 1998-106350P	P	19981030
US 1998-108184P	P	19981112
US 1999-123675P	P	19990309
US 1998-101693P	P	19980925
WO 1999-US16747	W	19990723

AB Polypeptides and peptides are disclosed which contain at least three amino acids randomly joined in a linear array, in which at least one of the three amino acids is an arom. amino acid, at least one of the three amino acids is a charged amino acid and at least one amino acid is an aliph. amino acid. In a preferred embodiment, the polypeptide contains three or four of the following amino acids: tyrosine, alanine, glutamic acid or lysine. According to the invention, the polypeptides bind to antigen-presenting cells, purified human lymphocyte antigens (HLA), and/or Copolymer 1-specific **T cells**. Morever, these polypeptides can be formulated into pharmaceutical compns. for treating autoimmune disease. Also disclosed are methods of treating an autoimmune disease in a mammal by administering a pharmaceutically

effective amt. of any one of the polypeptides or peptides.
REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 7 OF 21 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1999:529040 HCAPLUS
DOCUMENT NUMBER: 131:153743
TITLE: Novel **preventives/remedies** for **immunopathy**
INVENTOR(S): Sasaki, Takumi; Kimachi, Kazuhiko; Soejima, Kenji; Kimura, Yumi; Nozaki, Chikateru; Fujiyama, Yoshihide
PATENT ASSIGNEE(S): Juridical Foundation the Chemo-Sero-Therapeutic Research Institute, Japan
SOURCE: PCT Int. Appl., 39 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9940935	A1	19990819	WO 1999-JP638	19990215
W: AU, CA, CN, JP, KR, US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
CA 2320512	AA	19990819	CA 1999-2320512	19990215
AU 9923009	A1	19990830	AU 1999-23009	19990215
AU 746372	B2	20020418		
EP 1055429	A1	20001129	EP 1999-902905	19990215
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				

PRIORITY APPLN. INFO.: JP 1998-50137 A 19980215
WO 1999-JP638 W 19990215

AB The invention relates to **preventives/remedies** for **immunopathy** which contain as the active ingredient **modifications** of natural **Staphylococcus** aureus **enterotoxin B** (**SEB**), wherein at least one of the amino acid residues in the amino acid sequence of **SEB** has been substituted, or derivs. thereof, characterized in that these **modifications** or derivs. thereof have an effect of inhibiting the activation of **T cells** by undergoing interactions with the specific **V** . **beta**. component of **T cell** receptor (**TCR**) but not causing the elimination of **T cells** having the specific **V** .**beta**. component induced by natural **SEB** or recombinant wild **SEB**, thus exclusively depressing the immunol. response to **SEB**.

IT **210293-63-3, Enterotoxin B** (**Staphylococcus** aureus) **237074-87-2 237074-89-4 237074-94-1 237074-96-3 237074-98-5 237075-00-2 237075-02-4 237075-03-5 237075-04-6 237075-05-7 237075-06-8 237075-08-0**
RL: BAC (Biological activity or effector, except adverse); BSU

(Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(amino acid-**modified Staphylococcus enterotoxin B** as novel **preventives/remedies** for **immunopathy**)
REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 8 OF 21 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1999:201918 HCAPLUS
DOCUMENT NUMBER: 130:276742
TITLE: Thiazole derivatives as immunosuppressant
INVENTOR(S): Nakatsuka, Masashi; Okada, Shinichiro; Hashizuka, Takahiko; Nishikado, Fumio
PATENT ASSIGNEE(S): Sumitomo Pharmaceuticals Co., Ltd., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 16 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 11079993	A2	19990323	JP 1997-257839	19970905

PRIORITY APPLN. INFO.: JP 1997-257839 19970905
OTHER SOURCE(S): MARPAT 130:276742
AB Disclosed are novel immunosuppressants with thiazole-based structure. The thiazole derivs. selectively inhibit superantigen-induced proliferation of **T cell**, and are used for **treating** autoimmune diseases, e.g chronic rheumatoid **arthritis**, multiple sclerosis, and ulcerative colitis. Thus, 2-(4-Pyridyl)-4-(4-cyanophenyl)-thiazole was prepd. by using 4-cyanoacetophenone and thioisonicotinamide as reactants, and used for inhibiting **Staphylococcal enterotoxin B**-induced **T cell** proliferation as well as **treating** collagen-induced **arthritis**.

L6 ANSWER 9 OF 21 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1998:75220 HCAPLUS
DOCUMENT NUMBER: 128:153064
TITLE: **Prevention** of collagen-induced **arthritis** with the superantigen, **staphylococcal enterotoxin B**
AUTHOR(S): Sasaki, Takumi; Fujiyama, Yoshihide; Ide, Toshio; Kakimoto, Kiichi; Niwakawa, Mitsuyuki; Bamba, Tadao; Tokiyoshi, Sachio; Onoue, Kaoru
CORPORATE SOURCE: The Research and Development Department, Kikuchi Research Centre, The Chemo-Sero-Therapeutic Research Institute, Kumamoto, 869-12, Japan
SOURCE: Pathophysiology (1997), 4(1), 25-31
CODEN: PTHOE7; ISSN: 0928-4680
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB I.v. administration of **staphylococcal enterotoxin**

B (**SEB**) induced **T cell** tolerance in DBA/I mouse which is known to be susceptible to collagen-induced arthritis (CIA), a mouse model of human rheumatoid arthritis. After repeated administration of SEB, the proliferative response to SEB of spleen **T cells** was decreased. The SEB-reactive **V.beta**.8 **TCR+** **T cell** population in the treated mice was reduced only partially but the proliferative response of spleen **T cells** to anti-**V.beta**.8+ **TCR** monoclonal antibody was profoundly decreased, indicating that the tolerance to SEB is induced mainly by induction of the anergic state in **V.beta**.8 **TCR+** **T cells** and to some extent by the partial deletion of these lymphocytes. In SEB-treated mice, the incidence of CIA was decreased to about 20% of that of control mice. The severity of the disease in mice which developed CIA was also decreased in the SEB-treated mice. Furthermore, the proliferative response to type II collagen (CII) of the spleen **T cell** of disease-suppressed mice was impaired. The anti-CII IgG level in the serum of the SEB-treated mice was also decreased but only moderately. These results suggest the applicability of the superantigen-based therapy to **V.beta** .-restricted, **T cell**-dominated autoimmune diseases.

REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 10 OF 21 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1997:311257 HCAPLUS
DOCUMENT NUMBER: 126:288104
TITLE: Use of chloroquine to **treat** multiple sclerosis, cutaneous lymphoma, rheumatoid **arthritis**, and autoimmune disease and in a method for CD4+ **T-cell** depletion
INVENTOR(S): Pernis, Benvenuto G.
PATENT ASSIGNEE(S): Columbia University, USA
SOURCE: U.S., 12 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5624938	A	19970429	US 1994-276259	19940718

PRIORITY APPLN. INFO.: US 1994-276259 19940718

AB The invention provides a pharmaceutical compn. which comprises an amt. of chloroquine effective to block MHC Class I recycling and an amt. of a CD8+ **T-cell**-stimulatory agent effective to stimulate proliferation of CD8+ **T-cells** to a concn. such that the resulting CD8+ **T-cells** kill CD4+ **T-cells**, and a pharmaceutically acceptable carrier. The invention also provides a method for treating an autoimmune disease in a subject which comprises administering to the subject an amt. of chloroquine

effective to treat the autoimmune disease. Th invention provides a method for treating cutaneous lymphoma disease in a subject which comprises administering to the subject an amt. of chloroquine effective to treat the cutaneous lymphoma disease. Th invention further provides a method for **treating** rheumatoid **arthritis** in a subject which comprises administering to the subject an amt. of the pharmaceutical compn. of chloroquine and a CD8+ **T-cell**-stimulatory agent effective to **treat** rheumatoid **arthritis**. Finally, the invention provides a method of depleting CD4+ **T-cells** which comprises contacting to the cells an amt. of chloroquine effective to block MHC Class I recycling and a CD8+ **T-cell**-stimulatory agent in an amt. effective to stimulate proliferation of CD8+ **T-cells** to a concn. such that the resulting CD8+ **T-cells** kill CD4+ **T-cells**, so as to thereby deplete CD4+ **T-cells**.

L6 ANSWER 11 OF 21 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1996:491343 HCAPLUS
DOCUMENT NUMBER: 125:165519
TITLE: Inhibition of superantigen-induced proinflammatory cytokine production and inflammatory arthritis in MRL-lpr/lpr mice by a transcriptional inhibitor of TNF-.alpha.
AUTHOR(S): Edwards, Carl K., III; Zhou, Tong; Zhang, Jun; Baker, Tari J.; De, Mamata; Long, Richard E.; Borcherding, David R.; Bowlin, Terry L.; Bluethmann, Horst; Mountz, John D.
CORPORATE SOURCE: Dep. Immunol., Hoechst Marion Roussel, Cincinnati, OH, 45215, USA
SOURCE: Journal of Immunology (1996), 157(4), 1758-1772
CODEN: JOIMA3; ISSN: 0022-1767
PUBLISHER: American Association of Immunologists
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The authors used fas-defective MRL-lpr/lpr mice to study the effects of the staphylococcal enterotoxin superantigens on the development of autoimmune, inflammatory joint disease in animals that are susceptible to the development of rheumatoid arthritis-like disease. The authors show that systematic administration by a single i.p. injection of **staphylococcal enterotoxin B** (**SEB**; 10 .mu.g/mouse) caused a mild, inflammatory arthritis +30 days postchallenge in the knee joints of young (<2-mo-old) MRL-lpr/lpr mice, but not aged-matched MRL +/+ mice. In aged (>8-mo-old) MRL-lpr/lpr mice, but not in aged MRL +/+ mice, SEB caused a severe, inflammatory arthritis, as assessed histol., and systemic autoimmune disease, including glomerulonephritis and autoantibody prodn. Furthermore, in aged MRL-lpr/lpr mice, SEB but not heat-denatured SEB caused acute wt. loss and elevated levels of serum proinflammatory cytokines. Compared with highly purified peritoneal macrophages obtained from either aged MRL +/+, young MRL-lpr/lpr, or young MRL +/+, peritoneal macrophages obtained from aged MRL-lpr/lpr mice constitutively expressed 2-10-fold greater levels of TNF-.alpha., IL-1.beta., IL-6, and IL-10, and produced elevated amts. of these cytokines when treated in vitro with SEB. SEB-challenged aged MRL-lpr/lpr mice **treated** with anti-TNF mAb (100 .mu.g/mouse; every other

day), anti-**V.beta.**8 **TCR** mAb (250 .mu.g/mouse; every other day), or orally with the novel TNF-.alpha. inhibitor MDL 201,449A (9-[(1R, 3R)-trans-cyclopentan-3-ol] adenine; 25 mg/kg/day) exhibited reduced inflammatory **arthritis**, autoantibody formation, and serum TNF-.alpha. levels, but not IL-10 levels, after +30 days of **treatment**. Thus, SEB is an extremely potent macrophage-activating factor in vitro and in vivo, enhancing several aspects of autoimmune disease in MRL-lpr/lpr mice, and anti-TNF **therapies** may have potential use in inflammatory **arthritis**.

L6 ANSWER 12 OF 21 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1996:448300 HCAPLUS
DOCUMENT NUMBER: 125:132061
TITLE: The effect of SM-8849 on experimental arthritis in mice
AUTHOR(S): Nagai, Hiroichi; Takaoka, Yuko; Kuwabara, Kenji; Kamada, Hiroyuki; Kitagaki, Kunihiko
CORPORATE SOURCE: Department Pharmacology, Gifu Pharmaceutical University, Gifu, 205, Japan
SOURCE: Pharmacology (1996), 52(6), 377-386
CODEN: PHMGBN; ISSN: 0031-7012
PUBLISHER: Karger
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The effect of a novel thiazole deriv., SM-8849, on exptl. arthritis in mice was studied and compared to that of prednisolone. SM-8849 and prednisolone reduced the incidence and severity of type II collagen-induced arthritis in mice, as assayed by clin. observation and histopathol. studies. Although both agents inhibited type II collagen-induced delayed type hypersensitivity (DTH) in arthritic mice, SM-8849 did not affect the prodn. of humoral antibodies to type II collagen. To examine the inhibitory mechanism of SM-8849, the effects on **T cell**-dependent allergic inflammation were studied. SM-8849 clearly inhibited **T cell**-dependent reactions including **staphylococcal enterotoxin B** (**SEB**)-induced arthritis, **SEB**-induced CD25 expression on **T cells** and sheep red blood cell (SRBC)-induced DTH reaction. SM-8849, however, had no effect on the prodn. of humoral antibody forming cells in the spleen of mice immunized with SRBC. These results indicate that inhibition of type II collagen-induced arthritis by SM-8849 is mainly due to the inactivation of **T cells** that are related to DTH reaction.

L6 ANSWER 13 OF 21 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1996:425776 HCAPLUS
DOCUMENT NUMBER: 125:104592
TITLE: The effects of mesoporphyrin on experimental arthritis in mice
AUTHOR(S): Nagai, H.; Takaoka, Y.; Mori, H.; Matsuura, N.
CORPORATE SOURCE: Dep. Pharmacology, Gifu Pharmaceutical Univ., Gifu, 502, Japan
SOURCE: Inflammation Research (1996), 45(6), 293-298
CODEN: INREFB; ISSN: 1023-3830
PUBLISHER: Birkhaeuser
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The effects of mesoporphyrin, a novel porphyrin deriv., on type II collagen-induced arthritis in mice were studied. Mesoporphyrin (10-30 mg/kg) and prednisolone (5 mg/kg; ref. drug) reduced the incidence and severity of type II collagen-induced arthritis in mice, as assayed by clin. observation and histopathol. studies. Although both agents inhibited type II collagen-induced delayed type hypersensitivity in arthritic mice, only prednisolone inhibited humoral immunity to type II collagen. The effects of mesoporphyrin on **T cell** dependent allergic inflammation were examd., in order to study the mechanism by which it inhibits arthritis. **Staphylococcal enterotoxin B** (**SEB**; superantigen)-potentiated collagen-induced arthritis and sheep red blood cell-induced delayed type hypersensitivity reaction were clearly inhibited by mesoporphyrin. Moreover, the superantigen-induced CD-25 expression on **T cells** was inhibited by mesoporphyrin. These results indicate that mesoporphyrin inhibits type II collagen-induced arthritis by inhibiting the activation of **T cells**.

L6 ANSWER 14 OF 21 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1996:299918 HCAPLUS
DOCUMENT NUMBER: 124:340732
TITLE: Repopulation of blood lymphocyte sub-populations in rheumatoid **arthritis** patients **treated** with the depleting humanized monoclonal antibody, CAMPATH-1H
AUTHOR(S): Brett, S.; Baxter, G.; Cooper, H.; Johnston, J. M.; Tite, J.; Rapson, N.
CORPORATE SOURCE: Biology Div., Wellcome Res. Labs., Beckenham, Kent, UK
SOURCE: Immunology (1996), 88(1), 13-19
CODEN: IMMUAM; ISSN: 0019-2805
PUBLISHER: Blackwell
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Patients with severe rheumatoid **arthritis** who had failed **treatment** with conventional **therapies** were **treated** with a course of five or 10 daily i.v. infusions of CAMPATH-1H, a humanized antibody against the CD52 antigen, resulting in profound depletion of peripheral blood mononuclear cells. During the subsequent 18 mo, lymphocytes were analyzed for subpopulations by fluorescence-activated cell sorter (FACS) and for proliferation in response to polyclonal **T-cell** stimulation with anti-CD3 or **staphylococcal enterotoxin B** (**SEB**). Treatment resulted in almost complete depletion of lymphocytes from the blood followed by gradual repopulation. CD16+ natural killer (NK) cells and CD14+ monocytes returned to pretreatment levels within 1-2 mo. CD19+ B cells returned to within 50% of pre-treatment levels by day 66 and to within normal range by day 150, whereas CD8+ **T cells** recovered to 50% of pretreatment levels by day 66, but did not show any further increase during the rest of the study period. The most profound effects were on the CD4+ **T lymphocyte** sub-population, as the mean CD4+ count did not increase above 20% of pre-treatment level at any time during the study period (550 days), at all the doses tested. The **T cells** which initially repopulated the blood 1-2 mo after treatment, nearly all expressed the activation markers human

leukocyte antigen (HLA)-DR and CD45RO, although the percentage of **T cells** expressing these mols. gradually declined to normal levels over time. Proliferative responses to polyclonal **T-cell** stimulation (anti-CD3 and SEB) were also significantly reduced in the first few months after treatment, but recovered to pre-treatment levels by day 250. The relation between these observations and the clin. response is discussed.

L6 ANSWER 15 OF 21 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1996:98208 HCAPLUS
DOCUMENT NUMBER: 124:143273
TITLE: In vivo blockade of TNF-.alpha. by intravenous infusion of a chimeric monoclonal TNF-.alpha. antibody in patients with rheumatoid arthritis. Short term cellular and molecular effects
AUTHOR(S): Lorenz, Hanns-Martin; Antoni, Christian; Valerius, Thomas; Repp, Roland; Gruenke, Mathias; Schwerdtner, Nives; Nuesslein, Hubert; Woody, Jim; Kalden, Joachim R.; et al.
CORPORATE SOURCE: Dep. Internal Medicine, Univ. Erlangen-Nuremberg, Erlangen, Germany
SOURCE: Journal of Immunology (1996), 156(4), 1646-53
CODEN: JOIMA3; ISSN: 0022-1767
PUBLISHER: American Association of Immunologists
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Due to the unknown etiol. of **RA**, specific **treatment** is not available. Recently, in a double-blinded, placebo-controlled clin. trial, in vivo blockade of TNF-.alpha. by a single infusion of a chimeric TNF-.alpha.-blocking mAb, cA2, has proven to be highly effective in the **treatment** of **RA**. In parallel to this trial, the authors tested the consequences of cA2 infusion in ex vivo and in vitro expts. In this paper, the authors describe an increase in CD4+ and CD8+ **T lymphocyte** counts on day 1 and a marked decrease in monocyte counts preferentially on day 7 after cA2 treatment, without major changes in B lymphocyte or NK cell counts. In addn., the authors found an increased responsiveness of PBMC to CD28 mAb/PMA, but not to CD3 mAb, superantigen **staphylococcus enterotoxin B**, or PHA on day 1 after infusion. The increase in DNA synthesis of PBMC was paralleled by increased IL-2 mRNA and IL-4 mRNA expression and IL-2 protein secretion in culture supernatants after in vitro stimulation of PBMC with CD28 mAb/PMA. In PBMC, the authors did not find any significant changes in mRNA or protein expression of CD28 Ag or CD28 ligands, B7-1 and B7-2. Serum concns. of IL-1.beta., IL-6, and sol. CD14 were significantly diminished after in vivo TNF-.alpha. blockade. The authors did not see relevant changes in granulocyte function in vitro after cA2 infusion. Finally, the authors obsd. a statistically significant decrease in sICAM-1 mols. in the serum of patients treated with serum compared with that in the serum of subjects given placebo. This change in sICAM-1 concn. was evident on days 1 and 7 after the infusion of 10 mg/kg cA2, whereas it occurred only on day 7 in the serum of patients treated with the low dose (1 mg/kg) of cA2.

L6 ANSWER 16 OF 21 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1995:558376 HCAPLUS

DOCUMENT NUMBER: 122:288740
TITLE: **Staphylococcal enterotoxin B** increases the severity of type II collagen induced arthritis in mice
AUTHOR(S): Wooley, Paul H.; Cingel, Barbara
CORPORATE SOURCE: School of Medicine, Wayne State University, Detroit, MI, 48201, USA
SOURCE: Annals of the Rheumatic Diseases (1995), 54(4), 298-304
CODEN: ARDIAO; ISSN: 0003-4967
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The authors studied the influence of **T cell** subset changes on the development of exptl. arthritis, by using the bacterial superantigen **staphylococcal enterotoxin B** (**SEB**) to modulate the **T cell** repertoire during the arthritogenic response to type II collagen (CII) in vivo. DBA/1 mice were injected with SEB before immunization with CII, and assessed for the development of collagen induced arthritis (CIA) and an immune response to CII. Mice with established **arthritis** were also **treated therapeutically** with SEB. Flow cytometry was used to evaluate the effect of the therapy on **T cell** subsets and **T cell** receptor (**TCR**) **V.beta**. expression. Mice injected with SEB developed **arthritis** faster than saline **treated** control animals, and developed more severe clin. features. Mice **treated** with SEB after the onset of CIA also progressed more rapidly to a severe **arthritis** than mice **treated** with saline alone. The level of anti-CII antibody was not affected by SEB injection. Flow cytometric anal. of **TCR** expression in mice 21 days after injection of CII showed decreased expression of **V.beta**.6 and **V.beta**.8 cells in SEB treated mice, compared with collagen immunized control mice. Injection of SEB alone caused a decrease in **V.beta**.8, but not **V.beta**.6 **T cells** compared with the values in normal DBA/1 mice. No variations in the **T cell** repertoire were detected 70 days after CII immunization. Thus, **treatment** with the bacterial enterotoxin SEB before the induction of **arthritis** did not suppress the immunol. or **arthritogenic** response to CII in DBA/1 mice, despite the modulation of the **V.beta**.8 **T cell** subset. **Treatment** of mice with established **arthritis** using SEB provoked a more severe disease course.

L6 ANSWER 17 OF 21 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1994:570550 HCAPLUS
DOCUMENT NUMBER: 121:170550
TITLE: Method using **Staphylococcus enterotoxin B** for treating autoimmune diseases
INVENTOR(S): Ochi, Atsuo
PATENT ASSIGNEE(S): Mount Sinai Hospital Corp., Can.
SOURCE: Can. Pat. Appl., 81 pp.
CODEN: CPXXEB
DOCUMENT TYPE: Patent
LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CA 2084120	AA	19940531	CA 1992-2084120	19921130

PRIORITY APPLN. INFO.: CA 1992-2084120 19921130

AB A method of **treating** autoimmune diseases (multiple sclerosis, rheumatoid **arthritis**, etc.) assocd. with a predominance of **T-cells** expressing **V**. **beta**.8+ **T-cell** receptor comprises administering an amt. of **Staphylococcus enterotoxin B** (**SEB**) (or a deriv., analog, or active fragment thereof) effective to reduce the no. and/or inactivate **T-cells** expressing **V** .**beta**.8+ **T-cell** receptor whereby there is a decrease in disease activity. Methods are also claimed for using SEB to assay for **T-cells** expressing the **V.beta**.8+ **T-cell** receptor assocd. with autoimmune disease pathogenesis and for using SEB to down-regulate lymphokines (preferably tumor necrosis factor and/or interleukin-6).

L6 ANSWER 18 OF 21 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1994:555532 HCAPLUS
DOCUMENT NUMBER: 121:155532
TITLE: The model of arthritis induced by superantigen in mice
AUTHOR(S): Nagai, Hiroichi; Takaoka, Yuko; Kamada, Hiroyuki; Mori, Hiroshi
CORPORATE SOURCE: Dep. Pharmacology, Gifu Pharmaceutical Univ., Gifu, 502, Japan
SOURCE: Life Sciences (1994), 55(12), PL233-PL237
CODEN: LIFSAK; ISSN: 0024-3205
DOCUMENT TYPE: Journal
LANGUAGE: English

AB S.c. injection of **Staphylococcal enterotoxin B** (**SEB**) produced by **Staphylococcus** aureus, caused severe arthritis in DBA/1J mice which had been previously immunized with bovine type II collagen. The severity of this arthritis was dose dependent and prolonged joint inflammation with erosion of bone was obsd. Anti-type II collagen antibodies were detected in the serum of arthritic mice. Effector **T cells** against type II collagen were also detected by delayed type hypersensitivity in the skin. Moreover, a significant decrease in the ratio between **T cells** and B cells and an increase in the ratio between CD4+ cells and CD8+ cells was obsd. in spleen cells from arthritic mice. Prednisolone suppresses the induction and development of clin. signs of arthritis in mice. This evidence suggests that this exptl. **arthritis** model may provide a means to examine the role of superantigens and the efficacy of pharmacol. agents for the **treatment** of rheumatoid **arthritis**.

L6 ANSWER 19 OF 21 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1994:161425 HCAPLUS
DOCUMENT NUMBER: 120:161425
TITLE: **T cell** influence on

superantigen-induced arthritis in MRL-lpr/lpr mice

AUTHOR(S): Mountz, John D.; Zhou, Tong; Long, Richard E.; Bluethmann, Horst; Koopman, William J.; Edwards, Carl K., III

CORPORATE SOURCE: Dep. Med., Univ. Alabama, Birmingham, AL, 35294, USA

SOURCE: Arthritis & Rheumatism (1994), 37(1), 113-24
CODEN: ARHEAW; ISSN: 0004-3591

DOCUMENT TYPE: Journal

LANGUAGE: English

AB To define the influence of the **T cell** receptor (**TCR**) and the lpr autoimmune gene on the induction and progression of superantigen-induced arthritis in **V.beta**.8 transgenic MRL-lpr/lpr mice. The time to onset and the extent of synovial hyperplasia after the induction of arthritis by intraarticular injection of **staphylococcal enterotoxin B** (**SEB**) were compared in mice having **T cells** that bear the **V.beta**.8 transgene alone (**V.beta**.8 **TCR** transgenic MRL-+/+), the lpr gene without the **V.beta**.8 gene (nontransgenic MRL-lpr/lpr), both the **V.beta**.8 gene and the lpr gene (**V.beta**.8 transgenic MRL-lpr/lpr), or neither gene (nontransgenic MRL-+/+). Synovial hyperplasia was compared in **SEB**-injected **V.beta**.8 transgenic MRL-lpr/lpr mice after treatment with cyclosporin A (CSA), anti-**V.beta**.8 and anti-CD4 monoclonal antibodies, and in **V.beta**.8 transgenic MRL-lpr/lpr mice after injection of a non-**V.beta**.8-reactive superantigen, **staphylococcal** enterotoxin A (SEA). At day 30, increased synovial cells were obsd. in all SEB-treated mice, but the increase was greatest in the **V.beta**.8 transgenic MRL-lpr/lpr mice. **T cell** involvement was indicated by the inability of either heat-denatured SEB or SEA to induce severe **arthritis**, the redn. in the severity of the **arthritis** on systemic **treatment** with CSA or anti-**V.beta**.8, and the correlation of synovial hyperplasia with in vitro SEB reactivity of **T cells**. These observations suggest that superantigens can induce chronic arthritis and that the induction and progression of the arthritis requires an underlying **T cell** defect in anergy induction in addn. to exposure to the superantigen.

L6 ANSWER 20 OF 21 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 1993:5610 HCAPLUS

DOCUMENT NUMBER: 118:5610

TITLE: Medicament containing an agent inhibiting pathological apoptosis in vivo and applications and methods to select the agent.

INVENTOR(S): Ameisen, Jean Claude; Groux, Herve; Capron, Andre; Ameisen, Fabienne

PATENT ASSIGNEE(S): Pasteur Institut, Fr.; Institut Pasteur de Lille; Institut National de la Sante et da la Recherche Medicale (INSERM)

SOURCE: Fr. Demande, 26 pp.
CODEN: FRXXBL

DOCUMENT TYPE: Patent

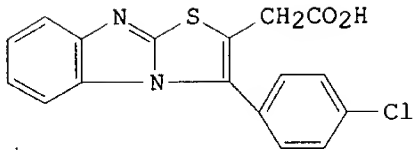
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
FR 2674433	A1	19921002	FR 1991-3739	19910327
FR 2674433	B1	19950519		
WO 9217193	A1	19921015	WO 1992-FR265	19920323
W: JP, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, MC, NL, SE				
EP 599845	A1	19940608	EP 1992-908880	19920323
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, MC, NL, SE				

PRIORITY APPLN. INFO.: FR 1991-3739 19910327
WO 1992-FR265 19920323

AB Medicaments contain an agent inhibiting pathol. apoptosis in vivo. The above agent is selected by contacting retroviral-infected cells with a cell activation agent (e.g. pokeweed mitogen) in the presence and absence of the test substance and comparing the proliferation of the 2 sets of cells. The medicament may contain an agent capable of blocking the reception or transduction of signal for the cellular suicide, an agent carrying or generating a cosignal permitting the cells to differentiate and multiply normally, or an agent capable of inhibiting the signals which render a cell susceptible to respond to activation towards pathol. apoptosis. The medicaments may be used to treat retroviral, esp. lentiviral, infections. Methods of detg. the deficiency in the immunol. repertoire of an individual to an infectious agent, of detg. the capacity of lymphocytes of an individual to respond to an infectious agent, of stimulating in vitro the lymphocytes of a patient infected with a retrovirus by treatment with anti-CD28 antigen antibody, and of selecting an agent inhibiting pathol. apoptosis in vivo are also disclosed. Antibody to CD28 antigen restored the capacity of lymphocytes from patients infected with HIV-1 virus to proliferate.

L6 ANSWER 21 OF 21 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1986:102138 HCAPLUS
DOCUMENT NUMBER: 104:102138
TITLE: Effects of WY-18,251 (3-(p-chlorophenyl)thiazolo[3,2-a]benzimidazole-2-acetic acid), levamisole and indomethacin on the generation of murine T suppressor cells in vitro
AUTHOR(S): Rogers, Christina M.; Rogers, Thomas J.; Gilman, Steven C.
CORPORATE SOURCE: Sch. Med., Temple Univ., Philadelphia, PA, 19140, USA
SOURCE: Journal of Immunopharmacology (1985), 7(4), 479-88
CODEN: JOIMD6; ISSN: 0163-0571
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I

AB In vitro culture of normal BALB/c spleen cells with **staphylococcal enterotoxin B** (**SEB**) activates antigen non-specific suppressor **T cells** (Ts) which can be assayed by their ability to suppress antibody prodn. in a plaque assay. Addn. of the exptl. immunomodulatory drug Wy-18,251 (I) [58433-11-7] (10-100 .mu.M) to cultures of spleen cells plus SEB significantly increased Ts activity relative to cultures without the drug. Similar results were obtained with levamisole [14769-73-4], but, in contrast, indomethacin [53-86-1] (0.1-10 .mu.M) inhibited SEB-induced suppressor cell activity. The ability of Wy-18,251 to augment Ts activity could be **therapeutically** useful in the **treatment** of those autoimmune diseases, such as rheumatoid **arthritis** and systemic lupus erythematosus, in which hyperactive B cell function is a characteristic feature.

(FILE 'MEDLINE, BIOSIS, EMBASE, WPIDS, JICST-EPLUS, JAPIO, PHIC, PHIN, TOXCENTER' ENTERED AT 09:42:32 ON 15 SEP 2003)

L7 6 SEA ABB=ON PLU=ON L4
L8 72 SEA ABB=ON PLU=ON L5
L9 5 SEA ABB=ON PLU=ON L8 AND (MUTAT? OR MODIF? OR MUTANT OR MUTAGEN? OR POLYMORPH? OR POLY MORPH?)
L10 7 SEA ABB=ON PLU=ON L7 OR L9
L11 5 DUP REM L10 (2 DUPLICATES REMOVED)

L11 ANSWER 1 OF 5 WPIDS COPYRIGHT 2003 THOMSON DERWENT on STN
DUPLICATE 1
ACCESSION NUMBER: 2003-468195 [44] WPIDS
DOC. NO. CPI: C2003-124784
TITLE: Producing recombinant bacterial superantigens useful as a biodefense vaccines and for treating sepsis or toxic shock, by culturing Escherichia coli cells of Master Cell Bank comprising the bacterial gene.
DERWENT CLASS: A97 B04 D16
INVENTOR(S): COFFMAN, J D; GIARDINA, S L; ZHU, J
PATENT ASSIGNEE(S): (USSH) US DEPT HEALTH & HUMAN SERVICES
COUNTRY COUNT: 101
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2003031471	A1	20030417	(200344)*	EN	66

RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SK SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ

NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ
UA UG US UZ VC VN YU ZA ZM ZW

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2003031471 A1		WO 2002-US31114	20020927

PRIORITY APPLN. INFO: US 2001-328017P 20011009
AN 2003-468195 [44] WPIDS
AB WO2003031471 A UPAB: 20030710
NOVELTY - Bacterial fermentation (M1) for producing a recombinant bacterial superantigen (SAg), involves culturing Escherichia coli cells of Master Cell Bank containing a construct comprising a recombinant bacterial SAg gene in a seed medium to yield a seed culture, culturing the cells to yield a production culture, inducing protein expression, disrupting the cells to yield a lysate, and recovering SAg protein from the lysate.

DETAILED DESCRIPTION - Bacterial fermentation (M1) for producing a recombinant bacterial superantigen (SAg), involves:

(1) culturing E. coli cells of Master Cell Bank containing an expression construct comprising a recombinant bacterial SAg gene operably linked to one or more expression control elements to direct expression of a recombinant SAg protein following induction in a sterile seed medium to yield a seed culture;

(2) culturing the recombinant E. coli cells from the seed culture in a sterile production medium to yield a production culture;

(3) inducing the recombinant E. coli cells of the production culture to express the recombinant SAg protein;

(4) disrupting the recombinant E. coli cells from the production culture to yield a lysate containing the recombinant SAg protein; and

(5) recovering the recombinant SAg from the lysate, where at least 50-60% of the recombinant SAg is recovered in a soluble form.

INDEPENDENT CLAIMS are also included for:

(1) high yield purification (M2) of a substantially purified SAg suitable for administration to a mammal, comprises:

(1) contacting a starting load material comprising the recombinant SAg and one or more contaminants to a hydrophobic interaction chromatography (HIC) substrate and washing to HIC substrate;

(2) collecting a flow through fraction from the HIC wash, the flow through fraction comprising HIC-purified recombinant SAg partially or completely separated from the contaminants;

(3) subjecting the HIC-purified recombinant SAg to a suitable buffer exchange to desalt the HIC- purified SAg fractions;

(4) subjecting the HIC-purified recombinant SAg following the buffer exchange to a cation exchange chromatography substrate under conditions sufficient to bind the recombinant SAg to the cation exchange substrate, while not substantially binding the contaminants; and

(5) eluting the recombinant SAg from the cation exchange substrate to provide a high yield substantially purified SAg protein suitable for administration to a mammalian subject; and

(2) a recombinant SAg composition produced by (M2).

ACTIVITY - **Antiarthritis**; Immunosuppressive; Antibacterial.

The potency of recombinant **staphylococcal enterotoxin B** (rSEB) was evaluated in a mouse protection assay. Pathogen-free BALB/c mice 10-12 weeks old were obtained from Harlan Sprague- Dawley. Mice were maintained under pathogen-free conditions and fed laboratory chow and water and libitum. Lipopolysaccharide (LPS) from E. coli O55:B5 was obtained and reconstituted with phosphate buffered saline (PBS). Recombinant **SEB** vaccine was diluted in 0.9% NaCl/50 mM glycine pH 8.5. Mice in groups of 10 were vaccinated intramuscularly with 5 or 20 micro g of recombinant **SEB** vaccine in 100 micro l of ALHYDROGEL (RTM) adjuvant or the adjuvant alone and boosted at 21 days in the same manner as described for the primary injection. Ten days after the booster vaccination, mice were challenged intraperitoneally with 10 LD50 of wild type **SEB** and LPS (75 micro g). Three days after challenge, the mice were scored for survivors. When immunized with 5 micro g of rSEB, 70% of the mice challenged with wild-type **SEB** were protected. 100% of mice were protected when challenged with wild-type **SEB** following immunization with 20 micro g of the recombinant vaccine protein.

MECHANISM OF ACTION - Vaccine.

USE - (M1) is useful for high yield production of a recombinant SAg, preferably a recombinant **staphylococcal enterotoxin B** (rSEB) which is **modified** by amino acid substitutions at position 89 (from tyrosine to alanine), position 45 (from leucine to arginine), and position 94 (tyrosine to alanine).

(M2) is useful for high yield purification of substantially purified recombinant SAg (claimed). The recombinant SAg is useful for **treating** disease and other conditions caused by bacterial SAgs, including food poisoning, bacterial **arthritis** and other autoimmune disorders, toxic shock syndrome, and insults attributed to the potential use of SAg biowarfare agents. The final rSEB product is immunogenic and protective against lethal aerosol challenge in a murine model predictive of immunogenic activity in other mammalian subjects, including human and non-human primates. rSAg is useful as an immunogen or vaccine agent, in particular as a biodefense vaccine, or for the **treatment** of sepsis or toxic shock.

ADVANTAGE - (M1) produces high yield of rSAg. The final product of the purification process is a highly purified rSAg composition satisfying clinical safety criteria and is highly immunogenic. The rSAgs produced by the methods are safe and the purity of the rSAg in the composition is greater than 99.5%.

Dwg.0/8

L11 ANSWER 2 OF 5 WPIDS COPYRIGHT 2003 THOMSON DERWENT on STN

ACCESSION NUMBER: 2000-505805 [45] WPIDS

DOC. NO. CPI: C2000-151790

TITLE: New treatment for inflammatory response mediated by endogenous substance P, useful for treating disease and infections including respiratory syncytial virus, by administration of anti-substance P antibody fragments.

DERWENT CLASS: B04

INVENTOR(S): ANDERSON, L J; MOORE, D D; TRIPP, R A

PATENT ASSIGNEE(S): (USSH) US DEPT HEALTH & HUMAN SERVICES
COUNTRY COUNT: 90
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2000043040	A1	20000727	(200045)*	EN	23

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
AU 2000024146 A 20000807 (200055)

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2000043040	A1	WO 2000-US1032	20000114
AU 2000024146	A	AU 2000-24146	20000114

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2000024146	A Based on	WO 2000043040

PRIORITY APPLN. INFO: US 1999-116835P 19990122
AN 2000-505805 [45] WPIDS
AB WO 200043040 A UPAB: 20000918
NOVELTY - A new treatment or prevention of a disease or syndrome caused by an inflammatory response mediated by endogenous substance P, comprises administering anti-substance P antibodies or their fragments.

ACTIVITY - Antiinflammatory; antiasthmatic; antirheumatic; **antiarthritic**; immunosuppressive; neuroprotective; antiviral; antibacterial. BALB/c mice acutely infected with respiratory syncytial virus (106 pfu) were i.n. treated with rabbit anti-substance P F(ab)2 antibody fragments to inhibit the biological activity of substance P. A dose-response experiment was performed to determine the amount of antibody fragments required to block the effects of substance P on intracellular generation of cytokines by CD3+ **T lymphocytes** and the effect of antibody fragments on cytokine production by **T lymphocytes** isolated from lungs was also examined. Antibodies were incubated overnight at 37 deg. C in citrate buffer containing 5 micro g pepsin per 1 micro g antibody before centrifugation at 10000 G for 30 minutes and resuspension in phosphate buffered saline. Anti-substance P F(ab)2 antibody fragments were separated from anti-substance P Fc fragments on a protein A column. Anaesthetized mice were treated 4 days post virus infection with 2, 20 or 200 micro g antibody fragments or with 200 micro g normal rabbit Ig (nIg) antibodies. Controls were not treated. **T lymphocytes** were collected from bronchoalveolar lavage specimens 18 or 36 hours after treatment and stained for intracellular cytokines using a procedure **modified** from the protocol of PharMingen. Cytokine transport was inhibited using 1

mu g/ml brefeldin (Sigma), **T lymphocytes** washed in PBS and the cell surface antigen stained with either anti CD4+ (RM4-5) or anti-CD8+ (53-6.7) antibody and fixed with 4% paraformaldehyde in D-PBS containing 1% BSA. Cells were then washed in PBS and the membranes permeabilized using saponin (Sigma). All intracellular antibodies were labelled with phycoerythrin (PharMingen). Anti-IL-2 (JES6-5H4), anti-IL-4 (BVD4-1D11), anti-IL-5 (TRFK5), anti-IL-6 (MP5-20F3) and anti-IFN approx. g (XMG1.2) antibodies were diluted in D-PBS containing 1% BSA and 0.1% saponin. Cells were stained on ice, washed with PBS, resuspended inn D-PBS containing 1% BSA and analyzed by flow-cytometry using a FACScan (Becton-Dickinson). 18 Hours post treatment, a single i.n. treatment of 200 micro g of the rabbit anti-substance P F(ab)2 antibody fragments per mouse induced approximately a 3-fold reduction in the intracellular cytokines IL-2, IL-4, IL-6 and IFN gamma made by **T lymphocytes** in the bronchoalveolar lavage fluid of the mice. The inhibitory effect was found to be dose-dependent, and specific for **T lymphocytes** of the bronchoalveolar lavage fluid, with no effect seen in spleens obtained from the mice. By 36 hours the only inhibitory effect seen was on IL-2 production.

MECHANISM OF ACTION - Endogenous substance P inhibitor.

USE - The method is useful for **treating** or **preventing** asthma, rheumatoid **arthritis**, infection associated with inflammatory bowel disease, rejection of allografts or other transplanted tissues or organs, virus-mediated bronchiolitis particularly respiratory syncytial virus, bacterial colitis, inflammation associated with chlamydial diseases, lung injury associated with **staphylococcal enterotoxin B**, inflammation due to cytomegalovirus or hepatitis B virus, pancreatitis, inflammation associated with multiple sclerosis or sepsis (claimed).

ADVANTAGE - The treatment of respiratory syncytial virus using the method of the invention is cheaper, easier and has less potential for adverse side-effects than prior art treatment using ribavirin.

Dwg.3/3

L11 ANSWER 3 OF 5 WPIDS COPYRIGHT 2003 THOMSON DERWENT on STN
DUPLICATE 2

ACCESSION NUMBER: 1999-508580 [42] WPIDS
DOC. NO. CPI: C1999-148570
TITLE: Treatment of immune disorders using a **modified** form of **Staphylococcus enterotoxin B** which does not induce **T-cell** proliferation.
DERWENT CLASS: B04 D16
INVENTOR(S): FUJIYAMA, Y; KIMACHI, K; KIMURA, Y; NOZAKI, C; SASAKI, T; SOEJIMA, K
PATENT ASSIGNEE(S): (KAGA) CHEMO-SERO-THERAPEUTIC RES INST; (KOWA) KOWA CO LTD
COUNTRY COUNT: 25
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 9940935	A1	19990819	(199942)*	JA	39

RW: AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE

W: AU CA CN JP KR US
AU 9923009 A 19990830 (200003)
EP 1055429 A1 20001129 (200063) EN
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
CN 1291106 A 20010411 (200140)
KR 2001034440 A 20010425 (200164)
AU 746372 B 20020418 (200238)
JP 2000531186 X 20021008 (200281)

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 9940935	A1	WO 1999-JP638	19990215
AU 9923009	A	AU 1999-23009	19990215
EP 1055429	A1	EP 1999-902905	19990215
		WO 1999-JP638	19990215
CN 1291106	A	CN 1999-802974	19990215
KR 2001034440	A	KR 2000-708218	20000727
AU 746372	B	AU 1999-23009	19990215
JP 2000531186	X	WO 1999-JP638	19990215
		JP 2000-531186	19990215

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 9923009	A	Based on	WO 9940935
EP 1055429	A1	Based on	WO 9940935
AU 746372	B	Previous Publ.	AU 9923009
		Based on	WO 9940935
JP 2000531186	X	Based on	WO 9940935

PRIORITY APPLN. INFO: JP 1998-50137 19980215
AN 1999-508580 [42] WPIDS
AB WO 9940935 A UPAB: 19991014
NOVELTY - Composition for the treatment and prevention of immune disorders containing as active component a **modified** **Staphylococcus enterotoxin B**, is new.
DETAILED DESCRIPTION - A composition for the treatment and prevention of immune disorders contains as active component **Staphylococcus** aureus **enterotoxin B** (**SEB**) **modified** by the substitution of one or more amino acid residues in its sequence, so as to inhibit its ability to induce proliferation of **T-cells** by interaction with the specific **V beta** component of the **T-cell** receptor, but not to cause elimination of **T-cells** having the specific **V beta** component of the **T-cell** receptor induced by natural (or recombinant wild-type) **SEB**.
USE - **Treatment** of immune disorders such as chronic rheumatoid **arthritis** and ulcerative colitis.
ADVANTAGE - The **modified** SEB are effective therapeutic agents without having the high toxicity of wild-type SEB.
Dwg.0/7

L11 ANSWER 4 OF 5 WPIDS COPYRIGHT 2003 THOMSON DERWENT on STN

ACCESSION NUMBER: 1997-087015 [08] WPIDS
DOC. NO. CPI: C1997-028210
TITLE: Treatment of diseases mediated by **T cells** having limited **V-beta** profile - comprises co-admin. of super-antigen or its deriv. and pharmacological agent(s) in a carrier.
DERWENT CLASS: B04
INVENTOR(S): BILL, J R
PATENT ASSIGNEE(S): (NEXS-N) NEXSTAR PHARM INC
COUNTRY COUNT: 69
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 9640235	A1	19961219	(199708)*	EN	44
RW: AT BE CH DE DK EA ES FI FR GB GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG					
W: AL AM AT AU AZ BB BG BR BY CA CH CN CZ DE DK EE ES FI GB GE HU IS JP KE KG KP KR KZ LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK TJ TM TR TT UA UG UZ VN					
AU 9659600	A	19961230	(199716)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 9640235	A1	WO 1996-US8193	19960531
AU 9659600	A	AU 1996-59600	19960531

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 9659600	A	Based on	WO 9640235

PRIORITY APPLN. INFO: US 1995-472547 19950607
AN 1997-087015 [08] WPIDS
AB WO 9640235 A UPAB: 19970220
Treatment of diseases mediated by **T cells** having a limited **Vbeta** profile comprises co-admin. of a superantigen or its deriv. (I) and pharmacological agent or agents (II) in a carrier. (I) specifically targets the pathogenic **Vbeta** expressing **T cells** for subsequent inactivation or deletion by the pharmacological agent(s).

(I) is a bacterial superantigen such as a **Staphylococcal** enterotoxin or toxic shock syndrome toxin, esp. **Staphylococcal enterotoxin B** (**SEB**). Alternatively, (I) is a **modified** superantigen fragment e.g. a bacterial superantigen deriv. or the (I) deriv. is a **mutated** superantigen or its fragment e.g. a bacterial superantigen deriv., esp. on **SEB** deriv. At least one (II) is a cytotoxic agent esp. methotrexate (MTX). At least one (II) controls potential cytokine toxicity. (II) may be an immunosuppressive e.g. a corticosteroid or dexamethasone. Esp., at least one subpopulation of **T cells** is deleted without activating the **T cells** to release toxic levels of cytokines.

USE - The method is used to **treat** autoimmune diseases such as rheumatoid **arthritis** and any disease caused by subpopulations of **T cells**. The admin. of additional agent(s) **prevents** or ameliorates toxic cytokine release eg. as occurs in toxic shock syndrome. Admin. is pref. by injection or continuous infusion.
Dwg.0/11

L11 ANSWER 5 OF 5 MEDLINE on STN
ACCESSION NUMBER: 96322771 MEDLINE
DOCUMENT NUMBER: 96322771 PubMed ID: 8759766
TITLE: Inhibition of superantigen-induced proinflammatory cytokine production and inflammatory arthritis in MRL-lpr/lpr mice by a transcriptional inhibitor of TNF-alpha.
AUTHOR: Edwards C K 3rd; Zhou T; Zhang J; Baker T J; De M; Long R E; Borcherding D R; Bowlin T L; Bluethmann H; Mountz J D
CORPORATE SOURCE: Department of Immunology, Hoechst Marion Roussel, Cincinnati, OH 45215, USA.
CONTRACT NUMBER: PO1-AR-03555 (NIAMS)
RO1-AR-42547 (NIAMS)
VO1-AI-34568 (NIAID)
+
SOURCE: JOURNAL OF IMMUNOLOGY, (1996 Aug 15) 157 (4) 1758-72.
Journal code: 2985117R. ISSN: 0022-1767.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199609
ENTRY DATE: Entered STN: 19960924
Last Updated on STN: 19970203
Entered Medline: 19960917

AB We have used fas-defective MRL-lpr/lpr mice to study the effects of the staphylococcal enterotoxin superantigens on the development of autoimmune, inflammatory joint disease in animals that are susceptible to the development of rheumatoid arthritis-like disease. We show that systematic administration by a single i.p. injection of **staphylococcal enterotoxin B** (**SEB**; 10 micrograms/mouse) caused a mild, inflammatory arthritis +30 days postchallenge in the knee joints of young (< 2-mo-old) MRL-lpr/lpr mice, but not aged-matched MRL +/+ mice. In aged (> 8-mo-old) MRL-lpr/lpr mice, but not in aged MRL +/+ mice, SEB caused a severe, inflammatory arthritis, as assessed histologically, and systemic autoimmune disease, including glomerulonephritis and autoantibody production. Furthermore, in aged MRL-lpr/lpr mice, SEB but not heat-denatured SEB caused acute weight loss and elevated levels of serum proinflammatory cytokines. Compared with highly purified peritoneal macrophages obtained from either aged MRL +/+, young MRL-lpr/lpr, or young MRL +/+, peritoneal macrophages obtained from aged MRL-lpr/lpr mice constitutively expressed 2- to 10-fold greater levels of TNF-alpha, IL-1 beta, IL-6, and IL-10, and produced elevated amounts of these cytokines when treated in vitro with SEB. SEB-challenged aged MRL-lpr/lpr mice **treated** with anti-TNF mAb (100 micrograms/mouse; every other day), anti-**V beta** 8 **TCR** mAb (250 micrograms/mouse; every other day), or orally with the

novel TNF-alpha inhibitor MDL 201,449A (9-[(1R, 3R)-trans-cyclopentan-3-ol] adenine; 25 mg/kg/day) exhibited reduced inflammatory **arthritis**, autoantibody formation, and serum TNF-alpha levels, but not IL-10 levels, after +30 days of **treatment**. These data suggest that SEB is an extremely potent macrophage-activating factor in vitro and in vivo, enhancing several aspects of autoimmune disease in MRL-lpr/lpr mice, and that anti-TNF **therapies** may have potential use in inflammatory **arthritis**.

(FILE 'MEDLINE' ENTERED AT 09:48:41 ON 15 SEP 2003)

L12 8357 SEA FILE=MEDLINE ABB=ON PLU=ON ENTEROTOXINS/CT
L13 17628 SEA FILE=MEDLINE ABB=ON PLU=ON STAPHYLOCOCCUS/CT
L14 543 SEA FILE=MEDLINE ABB=ON PLU=ON L12 AND L13
L16 12 SEA FILE=MEDLINE ABB=ON PLU=ON L14 AND (THERAPY OR THERAPEUTIC USE)/CT

L16 ANSWER 1 OF 12 MEDLINE on STN
AN 2003200584 MEDLINE
TI Preparation of a superantigen-adsorbing device and its superantigen removal efficacies in vitro and in vivo.
AU Miwa Keishi; Fukuyama Mayumi; Ida Nobuo; Igarashi Hideo; Uchiyama Takehiko
SO INTERNATIONAL JOURNAL OF INFECTIOUS DISEASES, (2003 Mar) 7 (1) 21-6. Journal code: 9610933. ISSN: 1201-9712.
AB OBJECTIVE: A new superantigen-adsorbing device (SAAD) was developed, and its characteristics and efficacy in septic animals were evaluated. METHODS: The SAAD was prepared by stepwise chemical modification of a polystyrene-based composite fiber reinforced with polypropylene. Adsorption affinities for several factors and the biological effect of superantigen (SAg) removal were measured in vitro. Also, superantigen-infused rabbits were treated with SAAD, and the efficacy was evaluated in vivo. RESULTS: When the SAAD was evaluated for its ability to adsorb SAg in human plasma (1 ng/mL each), the adsorption rates were 74%, 76% and 85% for staphylococcal enterotoxins A, B and C, respectively, and 80% and 72% for toxic shock syndrome toxin-1 (TSST-1) and streptococcal pyrogenic exotoxin A, respectively. In addition, the SAAD showed some affinity towards other molecules, such as streptococcal pyrogenic exotoxin B, beta2-microglobulin, and vancomycin. Residual activities in whole blood samples containing TSST-1 (1 ng/mL) after incubation with the SAAD were 125 pg/mL for tumor necrosis factor alpha (TNF-alpha) production, and 359 pg/mL for interleukin-8 (IL-8) production (the initial activities: 194 pg/mL for TNF-alpha production, and 1029 pg/mL for IL-8 production). When TSST-1/lipopolysaccharide (LPS)-infused rabbits were subjected to extracorporeal blood purification with a SAAD column, 50% of the animals survived for a 14-day period after the infusion. In contrast, all control animals died within 3 days after the infusion. CONCLUSION: These results indicate that the SAg-adsorbing device may be useful in treating SAg-related diseases.

L16 ANSWER 2 OF 12 MEDLINE on STN
AN 2001494225 MEDLINE
TI Analysis of the epitopes on staphylococcal enterotoxin A responsible for emetic activity.
AU Hu D L; Omoe K; Saleh M H; Ono K; Sugii S; Nakane A; Shinagawa K
SO JOURNAL OF VETERINARY MEDICAL SCIENCE, (2001 Mar) 63 (3) 237-41.

Journal code: 9105360. ISSN: 0916-7250.

AB To identify which region of staphylococcal enterotoxin A (SEA) is responsible for the emetic activity, twelve synthetic peptides corresponding to the entire SEA amino acid sequence and their respective anti-peptide antibodies were prepared and tested. The anti-peptide antibodies were tested for neutralization of SEA-induced emesis in Suncus murinus (Shrew mouse). The results indicate that SEA-induced emesis was neutralized by the mixture of three anti-peptide antibodies to A-7 (corresponding to amino acid residues 121-140), A-8 (141-160) and A-9 (160-180). These findings suggest that the regions corresponding to residues 121-180 may be the epitopes responsible for the emetic activity of SEA.

L16 ANSWER 3 OF 12 MEDLINE on STN
AN 2001200470 MEDLINE
TI Antagonistic effects of the staphylococcal enterotoxin a mutant, SEA(F47A/D227A), on psoriasis in the SCID-hu xenogeneic transplantation model.
AU Boehncke W H; Hardt-Weinelt K; Nilsson H; Wolter M; Dohlsten M; Ochsendorf F R; Kaufmann R; Antonsson P
SO JOURNAL OF INVESTIGATIVE DERMATOLOGY, (2001 Apr) 116 (4) 596-601. Journal code: 0426720. ISSN: 0022-202X.
AB Psoriasis is a T-cell-mediated immune dermatosis probably triggered by bacterial superantigens. This pathomechanism has been experimentally reproduced in a SCID-hu xenogeneic transplantation model. We analyzed the effects of different bacterial superantigens on the induction of psoriasis in this model. Staphylococcal enterotoxin B and exfoliative toxin triggered the onset of psoriasis when administered repetitively intracutaneously over a period of 2 wk, whereas staphylococcal enterotoxin A representing a distinct subfamily of staphylococcal enterotoxins only mimicked certain aspects of psoriasis. The biologic effects of staphylococcal enterotoxin A were more pronounced when a mutated form, SEA(H187A), of this superantigen with reduced affinity to major histocompatibility complex class II was coinjected. Another mutated variant, SEA(F47A/D227A), exhibiting no measurable major histocompatibility complex class II affinity blocked the effects triggered by wild-type staphylococcal enterotoxin A when injected in a 10-fold higher dose. Inhibition was specific as induction of psoriasiform epidermal changes by staphylococcal enterotoxin B could not be blocked. As staphylococcal enterotoxin A, in contrast to the other superantigens tested, is capable of inducing epidermal thickening but not the typical appearance of psoriasis, we conclude that bacterial superantigens may differ with regard to their effects on human nonlesional psoriatic skin. Staphylococcal-enterotoxin-A-mediated effects were blocked by a genetically engineered superantigen highlighting the potential therapeutic use of mutated superantigens.

L16 ANSWER 4 OF 12 MEDLINE on STN
AN 96409479 MEDLINE
TI The effects of mesoporphyrin on experimental arthritis in mice.
AU Nagai H; Takaoka Y; Mori H; Matsuura N
SO INFLAMMATION RESEARCH, (1996 Jun) 45 (6) 293-8. Journal code: 9508160. ISSN: 1023-3830.
AB The effects of mesoporphyrin, a novel porphyrin derivative, on type II collagen-induced arthritis in mice were studied. Mesoporphyrin (10-30 mg/kg) and prednisolone (5 mg/kg; reference drug) reduced the

incidence and severity of type II collagen-induced arthritis in mice, as assayed by clinical observation and histopathological studies. Although both agents inhibited type II collagen-induced delayed type hypersensitivity in arthritic mice, only prednisolone inhibited humoral immunity to type II collagen. The effects of mesoporphyrin on T cell dependent allergic inflammation were examined, in order to study the mechanism by which it inhibits arthritis. Staphylococcal enterotoxin B (SEB; superantigen)-potentiated collagen-induced arthritis and sheep red blood cell-induced delayed type hypersensitivity reaction were clearly inhibited by mesoporphyrin. Moreover, the superantigen-induced CD-25 expression on T cells was inhibited by mesoporphyrin. These results indicate that mesoporphyrin inhibits type II collagen-induced arthritis by inhibiting the activation of T cells.

L16 ANSWER 5 OF 12 MEDLINE on STN
AN 95325631 MEDLINE
TI Induction of responsiveness in superantigen-induced anergic T cells. Role of ligand density and costimulatory signals.
AU Heeg K; Wagner H
SO JOURNAL OF IMMUNOLOGY, (1995 Jul 1) 155 (1) 83-92.
Journal code: 2985117R. ISSN: 0022-1767.
AB The bacterial superantigen staphylococcal enterotoxin B (SEB) induces in vivo a state of anergy defined by the inability of V beta 8+ CD4+ T cells to produce IL-2 upon restimulation in vitro. However, restimulation in vivo triggers a burst of acutely released lymphokines including IL-2 and TNF, paralleled by up-regulation of lymphokine-specific mRNA. Since anergy as defined in vitro appears not to operate in vivo, we analyzed parameters able to induce responsiveness in anergic T cells. We show here that in vitro stimulation of anergic T cells with competent Ag-presenting cells induces responsiveness, provided the APC (activated B cells or dendritic cells) present high concentrations of SEB. Crosslinking of CD28 molecules on anergic T cells could substitute the requirement for competent APC. Quantitation of TCR threshold by determining the SEB concentrations able to trigger half-maximal T cell responses revealed that anergic and normal T cells exhibited the same TCR threshold for the expression of functional IL-2 receptors (IL-2R), yet the TCR threshold for induction of IL-2 production was 10- to 100-fold elevated in anergic T cells. TCR threshold for normal and anergic T cells was further dependent on the type of APC, i.e., costimulus-competent APC required 100-fold less SEB. The results indicate that extrinsic factors such as ligand concentration and costimulus competence of APC can overcome the heightened TCR threshold of anergic T cells, thus reverting anergy into responsiveness.

L16 ANSWER 6 OF 12 MEDLINE on STN
AN 92178014 MEDLINE
TI Development and design of a novel in vivo chamber implant for the analysis of microbial virulence and assessment of antimicrobial therapy.
AU Pike W J; Cockayne A; Webster C A; Slack R C; Shelton A P; Arbuthnott J P
SO MICROBIAL PATHOGENESIS, (1991 Jun) 10 (6) 443-50.
Journal code: 8606191. ISSN: 0882-4010.
AB An accurate reflection of the pathogenicity of microorganisms and the therapeutic effects of antimicrobial agents on their growth

necessitates testing within an in vivo environment. We have developed a novel diffusion chamber, incorporating two 0.22 microns membrane filters, for the growth of in vivo organisms. The chamber, which is implanted intraperitoneally into the rat, has an external sampling portal. This portal allows multiple and sequential sampling of the microbial inoculum without killing the rat, thus significantly reducing the total number of animals used in such studies. In addition, the chamber is superior to other reported implants since it is well tolerated, reusable, easily constructed and can be used within two days of implantation. Staphylococcus epidermidis and a toxic shock syndrome toxin-1 (TSST-1) producing strain of S. aureus have been successfully grown within in vivo chambers, with 10(8)-10(9) organisms per millilitre being recovered within 48 h. Scanning electron microscopy revealed clusters of staphylococci and fibrous material adhering to the inner surface of the filters, with numerous phagocytic cells attached to the outer side. Western immunoblotting indicated that higher levels of TSST-1 were produced by S. aureus grown in vivo as opposed to cells grown in vitro.

L16 ANSWER 7 OF 12 MEDLINE on STN
AN 85186029 MEDLINE
TI Experimental therapy of lethal poisoning due to combination of Vibrio thermostable direct hemolysin and staphylococcal enterotoxin.
AU Koike K; Fujiwara K
SO NIPPON EISEIGAKU ZASSHI. JAPANESE JOURNAL OF HYGIENE, (1984 Dec) 39 (5) 841-7.
Journal code: 0417457. ISSN: 0021-5082.

L16 ANSWER 8 OF 12 MEDLINE on STN
AN 81050298 MEDLINE
TI Potentiation of antitumor effect of virus-induced interferon by mouse immune interferon preparations.
AU Fleischmann W R Jr; Kleyn K M; Baron S
SO JOURNAL OF THE NATIONAL CANCER INSTITUTE, (1980 Nov) 65 (5) 963-6.
Journal code: 7503089. ISSN: 0027-8874.
AB In inbred DBA/2 mice, the antitumor activities of separate and combined preparations of mouse immune interferon and mouse virus-induced interferon on the development of P388 tumors were studied. Immune interferon alone (25 U/day) did not affect tumor development. Virus-induced interferon alone (25,000 U/day) delayed tumor development and increased survival time. The mouse immune interferon preparations significantly enhanced or potentiated the antitumor effects of mouse virus-induced interferon when the interferons were used in combined therapy.

L16 ANSWER 9 OF 12 MEDLINE on STN
AN 75142616 MEDLINE
TI [Staphylococci and mycoses as a cause of diarrhea]. Staphylokokken und Mykosen als Ursache einer Diarrhoe.
AU Hudemann H
SO ZEITSCHRIFT FUR DIE GESAMTE INNERE MEDIZIN UND IHRE GRENZGEBIETE, (1974 Aug 15) 29 (16) 666-9.
Journal code: 21730470R. ISSN: 0044-2542.

L16 ANSWER 10 OF 12 MEDLINE on STN
AN 73005796 MEDLINE
TI Pathophysiology of staphylococcal enterotoxin, type B, (SEB) toxemia

after intravenous administration to monkeys.
AU Beisel W R
SO TOXICON, (1972 Aug) 10 (5) 433-40.
Journal code: 1307333. ISSN: 0041-0101.

L16 ANSWER 11 OF 12 MEDLINE on STN
AN 68015744 MEDLINE
TI Mechanism study of the action of Malethamer in staphylococcus enterotoxin-induced diarrhea in monkeys.
AU Lin T M; Nash J F; Ensminger P W; Benslay D N
SO ARCHIVES INTERNATIONALES DE PHARMACODYNAMIE ET DE THERAPIE, (1967 Sep) 169 (1) 162-76.
Journal code: 0405353. ISSN: 0301-4533.

L16 ANSWER 12 OF 12 MEDLINE on STN
AN 68015742 MEDLINE
TI Experimental production of diarrhea and its prevention by Malethamer in monkeys.
AU Lin T M; Benslay D N; Ensminger P W; Nash J F
SO ARCHIVES INTERNATIONALES DE PHARMACODYNAMIE ET DE THERAPIE, (1967 Sep) 169 (1) 147-61.
Journal code: 0405353. ISSN: 0301-4533.

(FILE 'HCAPLUS, MEDLINE, BIOSIS, EMBASE, WPIDS, JICST-EPLUS, JAPIO, PHIC, PHIN, TOXCENTER' ENTERED AT 09:51:22 ON 15 SEP 2003)

- Author(s)

L17 45888 SEA ABB=ON PLU=ON ("TAKUMI S"? OR "SASAKI T"?)/AU
L18 106 SEA ABB=ON PLU=ON ("KIMACHI K"? OR "KAZUHIKO K"?)/AU
L19 1583 SEA ABB=ON PLU=ON ("KENJI S"? OR "SOEJIMA K"?)/AU
L20 25994 SEA ABB=ON PLU=ON ("KIMURA Y"? OR "YUMI K"?)/AU
L21 639 SEA ABB=ON PLU=ON ("CHIKATERU N"? OR "NOZAKI C"?)/AU
L22 1567 SEA ABB=ON PLU=ON ("YOSHIHIDE F"? OR "FUJIYAMA Y"?)/AU

L23 3 SEA ABB=ON PLU=ON L17 AND L18 AND L19 AND L20 AND L21 AND L22
L24 123 SEA ABB=ON PLU=ON L17 AND (L18 OR L19 OR L20 OR L21 OR L22)
L25 3 SEA ABB=ON PLU=ON L18 AND (L19 OR L20 OR L21 OR L22)
L26 22 SEA ABB=ON PLU=ON L19 AND (L20 OR L21 OR L22)
L27 3 SEA ABB=ON PLU=ON L20 AND (L21 OR L22)
L28 3 SEA ABB=ON PLU=ON L21 AND L22
L29 7 SEA ABB=ON PLU=ON (L24 OR L17 OR L18 OR L19 OR L20 OR L21 OR L22) AND L3
L30 26 SEA ABB=ON PLU=ON L23 OR L25 OR L26 OR L27 OR L29 OR L28
L31 10 DUP REM L30 (16 DUPLICATES REMOVED)

L31 ANSWER 1 OF 10 HCAPLUS COPYRIGHT 2003 ACS on STN DUPLICATE 1
ACCESSION NUMBER: 2003:42404 HCAPLUS
DOCUMENT NUMBER: 138:85606
TITLE: Recombinant production of ecarin capable of prothrombin and prethrombin-2 activation and purification by cation exchange and gel filtration chromatography
INVENTOR(S): Yonemura, Hiroshi; Imamura, Takayuki; Nakatake, Hiroshi; **Soejima, Kenji; Nozaki, Chikateru**
PATENT ASSIGNEE(S): Juridical Foundation the Chemo-Sero-Therapeutic Research Institute, Japan

SOURCE: PCT Int. Appl., 31 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003004647	A1	20030116	WO 2002-JP6770	20020704

W: AU, CA, CN, JP, KR, US
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR

PRIORITY APPLN. INFO.: JP 2001-206918 A 20010706

AB Recombinant ecarin capable of specifically activating prothrombin to meizothrombin, or prethrombin-2 to .alpha.-thrombin; and a process for large scale prodn. by genetic engineering, are disclosed. The method comprises: (1) transforming microbial or animal cells with an expression vector carrying a cDNA encoding ecarin integrated into downstream of a promoter, (2) culturing the host and collecting the ecarin thus produced and accumulated in the culture medium; and (3) purifying the ecarin from ecarin-contg. soln. thus collected and recovered. SV40 early promoter, late promoter, cytomegalovirus promoter, chicken .beta.-actin promoter, may be used. A signal sequence such as pelB signal, .alpha.factor signal, Ig signal SG-1 or C25, may also be used. CHO cells, mouse myeloma cells, BHK21 cells, 293 cells, or COS cells may be used. Recombinant ecarin was produced in a mammalian expression system using CHO cells and SP2/0 cells carrying the dihydrofolate reductase cDNA. The recombinant protein was purified using cation exchange chromatog. and gel filtration chromatog. The purified recombinant ecarin showed prothrombin activating catalytic properties identical to those of Echis carinatus-derived ecarin, cleaving Arg-Ile linkage of prothrombin.

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L31 ANSWER 2 OF 10 HCAPLUS COPYRIGHT 2003 ACS on STN DUPLICATE 2
ACCESSION NUMBER: 2003:42398 HCAPLUS
DOCUMENT NUMBER: 138:102943
TITLE: Human thrombin recombinant production by expression and purification of secreted human recombinant prethrombin-2 and its activation by ecarin
INVENTOR(S): Yonemura, Hiroshi; Imamura, Takayuki; Nakatake, Hiroshi; **Soejima, Kenji; Nozaki, Chikateru**
PATENT ASSIGNEE(S): Juridical Foundation the Chemo-Sero-Therapeutic Research Institute, Japan
SOURCE: PCT Int. Appl., 38 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

WO 2003004641	A1	20030116	WO 2002-JP6771	20020704

W: AU, CA, CN, JP, KR, US
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR

PRIORITY APPLN. INFO.: JP 2001-206919 A 20010706

AB A method for recombinant prodn. of human thrombin by expression and purifn. of prethrombin-2 and its activation by ecarin, is disclosed. Human prothrombin encoding cDNA placed under the regulation of a promoter is used to transform animal cells. SV40 early promoter, late promoter, cytomegalovirus promoter, chicken .beta.-actin promoter, may be used. A signal sequence such as Ig signal SG-1 or C25, may also be used. CHO cells, mouse myeloma cells, BHK21 cells, 293 cells, or COS cells may be used. A human prothrombin cDNA was engineered to obtain a cDNA coding for a secreted form of human prethrombin-2. The secreted prethrombin-2 was produced in a mammalian expression system using CHO cells and SP2/0 cells in which the dihydrofolate reductase gene has been deleted, and an expression vector carrying the dihydrofolate reductase cDNA. Methotrexate-induced gene amplification favored an efficient prodn. of the recombinant protein which accumulated in the culture medium of the CHO cells. Growth in suspension of the stable transformants in an airlift fermenter resulted in the prodn. of 25 mg/L recombinant prethrombin-2. The recombinant protein was purified using single-step affinity chromatog. on a recombinant-hirudin column and activated by agarose gel-immobilized ecarin. All purified recombinant prethrombin-2 was activated and the generated recombinant thrombin showed catalytic properties identical to those of plasma-derived .alpha.-thrombin.

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L31 ANSWER 3 OF 10 HCAPLUS COPYRIGHT 2003 ACS on STN DUPLICATE 3

ACCESSION NUMBER: 2002:849833 HCAPLUS
DOCUMENT NUMBER: 137:365556
TITLE: Preparation of human Von willebrand factor (VWF) specific protease and the uses of protease in therapeutics
INVENTOR(S): **Soejima, Kenji**; Mimura, Noriko; Maeda, Hiroaki; **Nozaki, Chikateru**; Hamamoto, Takayoshi; Nakagaki, Tomohiro
PATENT ASSIGNEE(S): Juridical Foundation the Chemo-Sero-Therapeutic Research Institute, Japan
SOURCE: PCT Int. Appl., 144 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002088366	A1	20021107	WO 2002-JP4141	20020425

W: AU, CA, CN, JP, KR, US
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR

PRIORITY APPLN. INFO.: JP 2001-128342 A 20010425

JP 2001-227510 A 20010727
JP 2001-302977 A 20010928
JP 2002-17596 A 20020125

AB This invention provides a process of prepn. and characterization of a protease specific to Von willebrand factor (VWF) purified from human. The protease exhibits catalytic activity of cleaving of VWF at position 842Tyr-843Met and mol. wt. 105-160 kDa and 160-250 kDa on SDS PAGE under reduced and oxidized conditions. Partial VWF protease internal sequence, Leu-Leu-Val-Ala-Val, and N-terminal sequence Ala-Ala-Gly-Gly-Ile-Leu-His-Leu-Glu-Leu-Leu-Val-Ala-Val were used for design primers for cloning of full length cDNA for VWF. The invention also provides cDNA and protein sequences of VWF specific protease and tissue distribution of the protease. The human VWF specific protease can be used for treatment liver disease such as thrombotic thrombocytopenic purpura.

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L31 ANSWER 4 OF 10 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2002:8846 HCAPLUS
DOCUMENT NUMBER: 139:81118
TITLE: A novel human metalloprotease synthesized in the liver and secreted into the blood: possibly, the von Willebrand factor-cleaving protease?. [Erratum to document cited in CA136:163110]
AUTHOR(S): **Soejima, Kenji**; Mimura, Noriko; Hirashima, Masaki; Maeda, Hiroaki; Hamamoto, Takayoshi; Nakagaki, Tomohiro; **Nozaki, Chikateru**
CORPORATE SOURCE: First Research Department, The Chemo-Sero-Therapeutic Research Institute, Kumamoto, 869-1298, Japan
SOURCE: Journal of Biochemistry (Tokyo, Japan) (2001), 130(5), 719
CODEN: JOBIAO; ISSN: 0021-924X
PUBLISHER: Japanese Biochemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The authors checked the raw sequencing data and found that position 3347 in Figure 4A on page 478 was actually "G". Therefore, positions 3346, 3347, and 3348 were not "AAA" representing Lys(K), but "AGA" representing Arg(R).

L31 ANSWER 5 OF 10 HCAPLUS COPYRIGHT 2003 ACS on STN DUPLICATE 4
ACCESSION NUMBER: 2001:884943 HCAPLUS
DOCUMENT NUMBER: 136:163110
TITLE: A novel human metalloprotease synthesized in the liver and secreted into the blood: possibly, the von Willebrand factor-cleaving protease?
AUTHOR(S): **Soejima, Kenji**; Mimura, Noriko; Hirashima, Masaki; Maeda, Hiroaki; Hamamoto, Takayoshi; Nakagaki, Tomohiro; **Nozaki, Chikateru**
CORPORATE SOURCE: First Research Department, The Chemo-Sero-Therapeutic Research Institute, Kumamoto, 869-1298, Japan
SOURCE: Journal of Biochemistry (Tokyo, Japan) (2001),

130(4), 475-480
CODEN: JOBIAO; ISSN: 0021-924X
PUBLISHER: Japanese Biochemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB We identified a novel metalloprotease which could be responsible for cleaving the Tyr842-Met843 peptide bond of von Willebrand factor (vWF). This metalloprotease was purified from Cohn Fraction-I ppt. of human pooled plasma by the combination of gel filtration, DEAE chromatog., and preparative PAGE in the presence of SDS. The NH2-terminal amino acid sequence of the isolated protein was: AAGGILHLELLVAVGPDVFQAHQEDTRRY. Based on this sequence, we searched human genomic and EST databases, and identified compatible nucleotide sequences. These results suggested that this protein is a novel metalloprotease, a member of the family of a disintegrin and metalloprotease with thrombospondin type-1 motifs (ADAMTS), and its genomic DNA was mapped to human chromosome 9q34. Multiple human tissue northern blotting anal. indicated that the mRNA encoding this protease spanned approx. 5 kilobases and was uniquely expressed in the liver. Furthermore, we detd. the cDNA sequence encoding this protease, and found that this protease was comprised of a signal peptide, a proregion followed by the putative furin cleavage site, a reprolysin-type zinc-metalloprotease domain, a disintegrin-like domain, a thrombospondin type-1 (TSP1) motif, a cysteine-rich region, a spacer domain, and COOH-terminal TSP1 motif repeats.

REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L31 ANSWER 6 OF 10 HCAPLUS COPYRIGHT 2003 ACS on STN DUPLICATE 5

ACCESSION NUMBER: 2001:694889 HCAPLUS
DOCUMENT NUMBER: 135:368376

TITLE: An efficient refolding method for the preparation of recombinant human prethrombin-2 and characterization of the recombinant-derived .alpha.-thrombin

AUTHOR(S): **Soejima, Kenji**; Mimura, Noriko; Yonemura, Hiroshi; Nakatake, Hiroshi; Imamura, Takayuki; **Nozaki, Chikateru**
CORPORATE SOURCE: First Research Department, The Chemo-Sero-Therapeutic Research Institute, Kumamoto, 869-1298, Japan

SOURCE: Journal of Biochemistry (Tokyo, Japan) (2001), 130(2), 269-277
CODEN: JOBIAO; ISSN: 0021-924X
PUBLISHER: Japanese Biochemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Human recombinant prethrombin-2 was produced in Escherichia coli. The expressed prethrombin-2 formed intracellular inclusion bodies from which the protein was refolded by a simple one-step diln. process in buffer consisting of 50 mM Tris-HCl, contg. 20 mM CaCl2, 500 mM NaCl, 1 mM EDTA, 600 mM arginine, 1 mM cysteine, 0.1 mM cystine, 10% (vol./vol.) glycerol, and 0.2% (w/v) Brij-58 at pH 8.5. After refolding, prethrombin-2 was purified by hirudin-based COOH-terminal peptide affinity chromatog., and then activated with Echis carinatus snake venom prothrombin activator (ecarin). The activated protein, .alpha.-thrombin, was then tested for several

activities including activity toward chromogenic substrate, release of fibrinopeptide A from fibrinogen, activation of protein C, and thrombin-activatable fibrinolysis inhibitor, reactivity with antithrombin, clotting activity, and platelet aggregation. The kinetic data showed no differences in activity between our recombinant .alpha.-thrombin and plasma-derived .alpha.-thrombin. The yield of refolded recombinant human prethrombin-2 was about 4-7% of the starting amt. of solubilized protein. In addn., the final yield of purified refolded protein was 0.5-1%, and about 1 mg of recombinant prethrombin-2 could be isolated from 1L of E. coli cell culture.

REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L31 ANSWER 7 OF 10 HCAPLUS COPYRIGHT 2003 ACS on STN DUPLICATE 6
ACCESSION NUMBER: 1999:529040 HCAPLUS
DOCUMENT NUMBER: 131:153743
TITLE: Novel **preventives/remedies** for **immunopathy**
INVENTOR(S): **Sasaki, Takumi; Kimachi, Kazuhiko; Soejima, Kenji; Kimura, Yumi; Nozaki, Chikateru ; Fujiyama, Yoshihide**
PATENT ASSIGNEE(S): Juridical Foundation the Chemo-Sero-Therapeutic Research Institute, Japan
SOURCE: PCT Int. Appl., 39 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9940935	A1	19990819	WO 1999-JP638	19990215
W: AU, CA, CN, JP, KR, US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
CA 2320512	AA	19990819	CA 1999-2320512	19990215
AU 9923009	A1	19990830	AU 1999-23009	19990215
AU 746372	B2	20020418		
EP 1055429	A1	20001129	EP 1999-902905	19990215
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				

PRIORITY APPLN. INFO.: JP 1998-50137 A 19980215
WO 1999-JP638 W 19990215

AB The invention relates to **preventives/remedies** for **immunopathy** which contain as the active ingredient modifications of natural **Staphylococcus** aureus **enterotoxin B** (**SEB**), wherein at least one of the amino acid residues in the amino acid sequence of **SEB** has been substituted, or derivs. thereof, characterized in that these modifications or derivs. thereof have an effect of inhibiting the activation of T cells by undergoing interactions with the specific V .beta. component of T cell receptor (TCR) but not causing the elimination of T cells having the specific V .beta. component induced by natural **SEB** or recombinant wild

SEB, thus exclusively depressing the immunol. response to **SEB**.

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L31 ANSWER 8 OF 10 JAPIO (C) 2003 JPO on STN
ACCESSION NUMBER: 1997-110704 JAPIO
TITLE: ORAL PREPARATION FOR **PREVENTING** AND **TREATING IMMUNOPATHY** DISEASE
INVENTOR: **SASAKI TAKUMI**; IDE TOSHIO; MORIYAMA TAKESHI; KOMORI KENJI; IMAGAWA YOSHITAKA; TOKIYOSHI YUKIO
PATENT ASSIGNEE(S): CHEMO SERO THERAPEUT RES INST
PATENT INFORMATION:

PATENT NO	KIND	DATE	ERA	MAIN IPC
JP 09110704	A	19970428	Heisei	A61K035-74

APPLICATION INFORMATION
STN FORMAT: JP 1995-297548 19951019
ORIGINAL: JP07297548 Heisei
PRIORITY APPLN. INFO.: JP 1995-297548 19951019
SOURCE: PATENT ABSTRACTS OF JAPAN (CD-ROM), Unexamined Applications, Vol. 1997

AN 1997-110704 JAPIO
AB PROBLEM TO BE SOLVED: To provide an oral preparation for **preventing** and **treating immunopathy** diseases such as rheumatoid **arthritis** or ulcerative colitis containing Staphylococcal-enterotoxins or their derivatives and is useful in **preventing** and **treating** these diseases.
SOLUTION: This oral preparation contains **Staphylococcal** -enterotoxins or their derivatives, preferably in an amount of 0.02-0.5μg each dose. The enterotoxins are preferably purified at such a level that it shows a single band in the gel electrophoresis. As the enterotoxins, is preferably cited **Staphylococcus** aureus **enterotoxins B**, A, C<SB>1</SB>, which bond to the VβT-cell antigen receptor. A liquid preparation in which the toxins or their derivatives are dissolved in physiological salt solution is preferred as an preparation form. The oral dose is 0.05-0.5μg/day on the basis of the enterotoxins and preferably given once or twice a day.
COPYRIGHT: (C)1997,JPO

L31 ANSWER 9 OF 10 HCAPLUS COPYRIGHT 2003 ACS on STN DUPLICATE 7
ACCESSION NUMBER: 1998:75220 HCAPLUS
DOCUMENT NUMBER: 128:153064
TITLE: **Prevention** of collagen-induced **arthritis** with the superantigen, **staphylococcal enterotoxin B**
AUTHOR(S): **Sasaki, Takumi**; **Fujiyama, Yoshihide**; Ide, Toshio; Kakimoto, Kiichi; Niwakawa, Mitsuyuki; Bamba, Tadao; Tokiyoshi, Sachio; Onoue, Kaoru
CORPORATE SOURCE: The Research and Development Department, Kikuchi

Research Centre, The Chemo-Sero-Therapeutic Research Institute, Kumamoto, 869-12, Japan
SOURCE: Pathophysiology (1997), 4(1), 25-31
CODEN: PTHOE7; ISSN: 0928-4680
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB I.v. administration of **staphylococcal enterotoxin B** (**SEB**) induced T cell tolerance in DBA/I mouse which is known to be susceptible to collagen-induced arthritis (CIA), a mouse model of human rheumatoid arthritis. After repeated administration of SEB, the proliferative response to SEB of spleen T cells was decreased. The SEB-reactive V.beta.8 TCR+ T cell population in the treated mice was reduced only partially but the proliferative response of spleen T cells to anti-V.beta.8+ TCR monoclonal antibody was profoundly decreased, indicating that the tolerance to SEB is induced mainly by induction of the anergic state in V.beta.8 TCR+ T cells and to some extent by the partial deletion of these lymphocytes. In SEB-treated mice, the incidence of CIA was decreased to about 20% of that of control mice. The severity of the disease in mice which developed CIA was also decreased in the SEB-treated mice. Furthermore, the proliferative response to type II collagen (CII) of the spleen T cell of disease-suppressed mice was impaired. The anti-CII IgG level in the serum of the SEB-treated mice was also decreased but only moderately. These results suggest the applicability of the superantigen-based therapy to V.beta.-restricted, T cell-dominated autoimmune diseases.
REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L31 ANSWER 10 OF 10 JAPIO (C) 2003 JPO on STN
ACCESSION NUMBER: 2002-306163 JAPIO
TITLE: METHOD OF PREPARING GENE-RECOMBINANT HUMAN THROMBIN USING ESCHERICHIA COIL AS HOST
INVENTOR: **SOEJIMA KENJI**; YONEMURA HIROSHI; NAKATAKE HIROSHI; IMAMURA TAKAYUKI; **NOZAKI CHIKAHIDE**
PATENT ASSIGNEE(S): CHEMO SERO THERAPEUT RES INST
PATENT INFORMATION:

PATENT NO	KIND	DATE	ERA	MAIN IPC
JP 2002306163	A	20021022	Heisei	C12N009-74

APPLICATION INFORMATION
STN FORMAT: JP 2001-113253 20010411
ORIGINAL: JP2001113253 Heisei
PRIORITY APPLN. INFO.: JP 2001-113253 20010411
SOURCE: PATENT ABSTRACTS OF JAPAN (CD-ROM), Unexamined Applications, Vol. 2002
AN 2002-306163 JAPIO
AB PROBLEM TO BE SOLVED: To provide a method of preparing gene-recombinant human thrombin by use of Escherichia coli as a host and improve the efficiency of the steps of the recovery of the inclusion bodies of human prothrombin as an expression product of Escherichia coli, the solubilization thereof and the rewinding. SOLUTION: The steps of the inclusion body recovery, the

solubilization of the inclusion body and the rewinding are carried out by the following operations: (1) the inclusion bodies are dispersed in the solubilization buffer; (2) the solubilization by crushing with ultrasonic wave or physical shearing force; and (3) dilution into refolding buffer solution. Desired recombinant thrombin preparation is given that can substitute the conventional thrombin preparations originating from bovine blood or human plasma.

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-Key terms

Set Items Description
S1 2567 ((ENTEROTOXIN OR ENTERO(W)TOXIN)(W)B OR SEB)(S)STAPHYLOCOC-C?
S2 300 S1 AND (RA(10N)ARTHRIT? OR ARTHRIT? OR ANTIARTHRIT? OR IMMUNOPATH? OR IMMUN??(W)PATH???)
S3 39 S1 AND ((RA(10N)ARTHRIT? OR ARTHRIT? OR IMMUNOPATH? OR IMMUN??(W)PATH???)(10N)(TREAT? OR THERAP? OR PREVENT? OR REMED?) OR ANTIARTHRIT?)
S4 26 RD (unique items)
>>>No matching display code(s) found in file(s): 65, 113

4/3,AB/1 (Item 1 from file: 144)
DIALOG(R)File 144:Pascal
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15921642 PASCAL No.: 03-0061752
SSR125329A, a high affinity sigma receptor ligand with potent anti-inflammatory properties
BOURRIE Bernard; BRIBES Estelle; DE NYS Nathalie; ESCLANGON Martine; GARCIA Laurent; GALIEGUE Sylvaine; LAIR Pierre; PAUL Raymond; THOMAS Corinne; ERES Jean-Claude Verni; CASELLAS Pierre
Sanofi-Synthelabo Recherche, Department of Immunology-Oncology, 371 rue du Professeur Blayac, 34184 Montpellier, France
Journal: European journal of pharmacology, 2002, 456 (1-3) 123-131
Language: English
SSR125329A (((Z)-3-(4-Adamantan-2-yl-3,5-dichloro-phenyl)-allyl)-cyclohexyl-ethyl-amine) is a new ligand exhibiting high affinity for sigma SUB 1 and sigma SUB 2 receptors and for the human DELTA 8- DELTA 7-sterol isomerase. Here we show that this molecule has potent immunoregulatory properties both in vitro and in vivo. SSR125329A inhibited *staphylococcal"** *enterotoxin"** *B"** -induced mouse splenocyte proliferation in vitro, whereas in vivo it enhanced lipopolysaccharide-induced systemic release of interleukin-10 while

simultaneously inhibiting tumor necrosis factor-alpha (TNF-a) synthesis. It also prevented graft-versus-host disease in B6D2F1 mice and protected Mrl/lpr mice against the development of its spontaneous rheumatoid-like syndrome. There is high interplay of pro- and anti-inflammatory cytokines in inflammatory processes, particularly in human rheumatoid arthritis. The results of this study provide substantial evidence that sigma receptor ligands may represent a new effective approach for rheumatoid *arthritis"** *treatment"**.

4/3,AB/2 (Item 2 from file: 144)
DIALOG(R)File 144:Pascal

14642964 PASCAL No.: 00-0314176
In vitro and in vivo inhibition of activation induced T cell apoptosis by bucillamine
OKAZAKI H; SATO H; KAMIMURA T; HIRATA D; IWAMOTO M; YOSHIO T; MIMORI A; MASUYAMA J I; KANO S; MINOTA S
Division of Clinical Immunology, Jichi Medical School, TochigiKen, Japan
Journal: Journal of rheumatology, 2000, 27 (6) 1358-1364
Language: English
Objective. To investigate the mechanism of autoimmune phenomena, occasionally seen in patients with rheumatoid *arthritis"** *treated"** with bucillamine (BUC) and D-penicillamine (D-Pen), by evaluating their effects on apoptosis of T cells induced by T cell receptor activation or dexamethasone. Methods. In vitro apoptosis was induced in a T cell hybridoma (SSP3.7) and a B cell line (WEHI 231) by activation of respective receptors or dexamethasone, in the presence or absence of BUC or D-Pen. In vivo apoptosis was induced in BALB/c mice by *staphylococcal"** *enterotoxin"** *B"** (*SEB"**), with or without BUC or D-Pen, and thymocytes were examined for it by FACS. Results. Stimulation with anti-CD3 and dexamethasone induced apoptosis in 72% and 71% of SSP3.7 cells, respectively. However, only 16% of SSP3.7 cells became apoptotic by anti-CD3 when BUC was added to the culture media. By contrast, 80% of SSP3.7 cells became apoptotic when stimulated by dexamethasone, even in the presence of BUC. BUC did not affect apoptosis of WEHI 231 cells induced by anti-IgM. Although SA981 (a metabolite of BUC) inhibited apoptosis of SSP3.7 cells induced by anti-CD3, D-Pen did not. BUC, SA981, or D-Pen did not significantly influence the level of interleukin 2 secretion stimulated by anti-CD3. In contrast, both BUC and D-Pen inhibited apoptosis of V beta 8+ thymocytes induced in vivo by *SEB"** superantigen. Neither BUC nor D-Pen significantly changed the number of CD4+CD8+ thymocytes in BALB/c mice injected with dexamethasone. Conclusion. BUC decreased, while D-Pen did not, the apoptosis of T cells stimulated by anti-CD3 in vitro, although they both inhibited the deletion of immature thymocytes reactive with *SEB"** in vivo. This may explain autoimmune phenomena sometimes seen during the treatment of rheumatic patients with these drugs.

4/3,AB/3 (Item 3 from file: 144)
DIALOG(R)File 144:Pascal

14410307 PASCAL No.: 00-0066231
PEGylated recombinant human soluble tumour necrosis factor receptor type I (r-Hu-sTNF-RI) : novel high affinity TNF receptor designed for chronic inflammatory diseases
Advances in targeted therapies: TNF alpha blockade in clinical practice
EDWARDS C K III
BREEDVELD F C, ed; KALDEN J R, ed; SMOLEN J S, ed
Department of Product Development, Amgen Inc, One Amgen Center Drive, MS: 27-5-A, Thousand Oaks, CA 91320-1789, United States
University of Leiden, Netherlands; University of Erlangen, Germany; University of Vienna, Austria
Journal: Annals of the rheumatic diseases, 1999, 58 (SUP1) I73-I81
Language: English
The proinflammatory cytokine, tumour necrosis factor alpha (TNF alpha) has been show to play a pivotal part in mediating acute and chronic inflammation. The activities of TNF alpha are modulated by the proteolytic shedding of the soluble extracellular domains of the two TNF receptors, p55 sTNF-RI and p75 sTNF-RII. Amgen Inc has cloned and expressed a recombinant form of a natural inhibitor of TNF alpha , referred to as recombinant human soluble TNF receptor type I (r-Hu-sTNF-RI, sTNF-RI). sTNF-RI is an E coli recombinant, monomeric form of the soluble TNF-type I receptor. A high molecular weight polyethylene glycol (PEG) molecule is attached at the N-terminus position to form the molecule intended for clinical evaluations (PEG sTNF-RI). Preclinical studies to date demonstrate that PEG sTNF-RI is efficacious in rodent models of chronic inflammatory disease including rheumatoid arthritis and Crohn's disease at doses as low as 0.3 mg/kg given every other day. This dose results in plasma concentrations of 0.3 to 0.5 mu g/ml. Higher doses with correspondingly higher plasma concentrations yield higher efficacy. It has also demonstrated efficacy in E coli lipopolysaccharide, and *Staphylococcus"** *enterotoxin"** *B"** mediated models of acute inflammation in rodents and primates. Pharmacokinetic studies in mice, rats, cynomolgus monkeys, baboons, and chimpanzees have been conducted with PEG sTNF-RI. Absorption from a subcutaneous dose was slow, with the time to reach maximal plasma concentrations of 24-48 hours in rats, and in monkeys, and 3-29 hours in chimpanzees. The initial volume of distribution of PEG sTNF-RI was essentially equivalent to that of plasma (40 ml/kg). This suggests the protein does not appear to extensively distribute from the systemic circulation with a volume of distribution at steady state (Vss) less than 200 ml/kg in all species studied. These results are consistent with previous experience with PEGylated proteins in which PEGylation decreases both the rate of absorption and the plasma clearance of human recombinant proteins in animals and humans. The use of a PEG molecule will probably provide a more advantageous dosing schedule (that is, less frequent dosing) for the patient compared with a non-PEG sTNF-RI.

4/3,AB/4 (Item 4 from file: 144)
DIALOG(R)File 144:Pascal

13569795 PASCAL No.: 98-0272028
Cyclosporin A and FK-506 inhibit development of superantigen-potentiated collagen-induced arthritis in mice
TAKAOKA Y; NAGAI H; TANAHASHI M; KAWADA K
Department of Pharmacology, Gifu Pharmaceutical University, 5-6-1

Mitahorahigashi, Gifu 502, Japan; Toray Industries, Inc, Basic Research Laboratories, Kanagawa, Japan; Department of Pathology, Gifu College of Medical Technology, Seki, Japan
Journal: General pharmacology, 1998, 30 (5) 777-782
Language: English
1. *Staphylococcal"** enterotoxine B (*SEB"**; superantigen) accelerated the onset of arthritis in mice preimmunized with type II collagen (*SEB"** -potentiated collagen-induced arthritis). Cyclosporin A and FK-506 inhibited the induction and development of clinical signs and histopathological changes of *SEB"**-potentiated collagen-induced arthritis in mice. 2. Simultaneously, both cyclosporin A and FK-506 inhibited the development of humoral and cellular immunity to type II collagen. 3. The expression of IL-2 receptor (CD25) by *SEB"** on splenocyte T cells from collagen-preimmunized mice was inhibited by both agents in ex vivo experimentation.

4/3,AB/5 (Item 5 from file: 144)
DIALOG(R)File 144:Pascal

12057848 PASCAL No.: 95-0254875
*Staphylococcal"** *enterotoxin"** *B"** increases the severity of type II collagen induced arthritis in mice
WOOLEY P H; CINGEL B
Wayne State univ. school medicine, dep. internal medicine, div. rheumatology, Detroit MI, USA
Journal: Annals of the rheumatic diseases, 1995, 54 (4) 298-304
Language: English
Objective-To observe the influence of T cell subset changes on the development of experimental arthritis, by using the bacterial superantigen staphylococcal *enterotoxin"** *B"** (*SEB"**) to modulate the T cell repertoire during the arthritogenic response to type II collagen (CII) in vivo. Methods-DBA/1 mice were injected with *SEB"** before immunisation with CII, and assessed for the development of collagen induced arthritis (CIA) and an immune response to CII. Mice with established *arthritis"** were also *treated"** *therapeutically"** with *SEB"**. Flow cytometry was used to evaluate the effect of the therapy on T cell subsets and T cell receptor (TCR) V beta expression. Results-Mice injected with *SEB"** developed *arthritis"** significantly faster than saline *treated"** control animals, and developed more severe clinical features. Mice treated with *SEB"** after the onset of CIA were also observed to progress more rapidly to a severe *arthritis"** than mice *treated"** with saline alone. The level of anti-CII antibody was not affected by *SEB"** injection. Flow cytometric analysis of TCR expression in mice 21 days after injection of CII showed decreased expression of V beta 6 and V beta 8 cells in *SEB"** treated mice, compared with collagen immunised control mice. Injection of *SEB"** alone caused a decrease in V beta 8, but not V beta 6 T cells compared with the values in normal DBA/1 mice. No significant variations in the T cell repertoire were detected 70 days after CII immunisation. Conclusions-*Treatment"** with the bacterial enterotoxin *SEB"** before the induction of *arthritis"** did not suppress the immunological or arthritogenic response to CII in DBA/1 mice, despite the modulation of the V beta 8 T cell subset. *Treatment"** of mice with established *arthritis"** using *SEB"** provoked a more severe disease course

4/3,AB/6 (Item 1 from file: 440)
DIALOG(R)File 440:Current Contents Search(R)

15974968 Document Delivery Available: 000182145600007 References: 47
TITLE: A model of human whole blood lymphokine release for in vitro and ex vivo use
AUTHOR(S): Hermann C; von Aulock S; Graf K; Hartung T (REPRINT)
AUTHOR(S) E-MAIL: Thomas.Hartung@uni-konstanz.de
CORPORATE SOURCE: Univ Konstanz, /D-78457 Constance//Germany/ (REPRINT); Univ Konstanz, /D-78457 Constance//Germany/
PUBLICATION TYPE: JOURNAL
PUBLICATION: JOURNAL OF IMMUNOLOGICAL METHODS, 2003, V275, N1-2 (APR 1), P 69-79
GENUINE ARTICLE#: 665XB
PUBLISHER: ELSEVIER SCIENCE BV, PO BOX 211, 1000 AE AMSTERDAM, NETHERLANDS
ISSN: 0022-1759
LANGUAGE: English DOCUMENT TYPE: ARTICLE

ABSTRACT: Endotoxin (lipopolysaccharide, LPS) inducible cytokine release by human whole blood is increasingly used to model inflammatory responses in vitro, to detect the presence of pyrogenic contaminations as well as to monitor disease states or immunomodulatory treatments ex vivo. However, the LPS-stimulated blood model primarily allows the assessment of monocyte responses. Here, a whole blood model was established which allows assessment of lymphocyte responses. Four different superantigens, namely *staphylococcal"** enterotoxin A and B (SEA, *SEB"**), toxic shock syndrome toxin-1 (TSST-1) or streptococcal exotoxin A (SPEA) were tested with respect to the induction of lymphokine release. All superantigens were capable of inducing significant amounts of the lymphokines interferon-gamma (IFNgamma), interleukin 2 (IL-2), IL-4, IL-5, IL- 13 and tumor necrosis factor beta (TNFbeta) after 72 h of incubation. Concentration-dependencies and kinetics were determined. Blood from 160 healthy donors was used to assess the variability of *SEB"**-inducible lymphokine release. Interindividual differences were more pronounced compared to LPS-inducible monokine release. However, the individual response was maintained when blood from six donors was tested once a week for 8 weeks, suggesting that the individual response represents a donor characteristic. The model appears to be suitable for the evaluation of immunomodulatory agents in vitro as well as ex vivo. (C) 2003 Elsevier Science B.V. All rights reserved.

4/3,AB/7 (Item 2 from file: 440)
DIALOG(R)File 440:Current Contents Search(R)

08167200 References: 33
TITLE: Superantigens: Their role in infectious diseases
AUTHOR(S): Stevens DL (REPRINT)
CORPORATE SOURCE: VET AFFAIRS MED CTR,/BOISE//ID/83702 (REPRINT); UNIV WASHINGTON,SCH MED/SEATTLE//WA/
PUBLICATION TYPE: JOURNAL
PUBLICATION: IMMUNOLOGICAL INVESTIGATIONS, 1997, V26, N1-2, P275-281
GENUINE ARTICLE#: WG293
PUBLISHER: MARCEL DEKKER INC, 270 MADISON AVE, NEW YORK, NY 10016
ISSN: 0882-0139
LANGUAGE: English DOCUMENT TYPE: ARTICLE

ABSTRACT: In the last 10 years many of the superantigens of the microbial world have been defined and the mechanisms of cellular interaction between lymphocytes and antigen presenting cells has been elucidated in great detail. The consequences of superantigen stimulation of the immune system, though less well defined, can be considered in three separate stages: T-cell proliferation, apoptosis, and recovery. Understanding these stages may explain why diverse superantigens may cause markedly different clinical processes ranging from acute shock to chronic *arthritis"** and may form the basis for novel *treatments"** of these diverse diseases.

4/3,AB/8 (Item 3 from file: 440)
DIALOG(R)File 440:Current Contents Search(R)

07731603 References: 97
TITLE: Inhibition of superantigen-induced proinflammatory cytokine production andinflammatory arthritis in MRL-lpr/lpr mice by a transcriptional inhibitor of TNF-alpha
AUTHOR(S): Edwards CK (REPRINT) ; Zhou T; Zhang J; Baker TJ; De M; Long RE; Borcherding DR; Bowlin TL; Bluethmann H; Mountz JD
CORPORATE SOURCE: AMGEN BOULDER,DEPT INFLAMMAT, 3200 WALNUT ST/BOULDER//CO/80301 (REPRINT); HOECHST MARION ROUSSEL,DEPT IMMUNOL/CINCINNATI//OH/45215; HOECHST MARION ROUSSEL,DEPT DISCOVERY CHEM/CINCINNATI//OH/45215; UNIV ALABAMA,DEPT MED/BIRMINGHAM//AL/35294; HOECHST MARION ROUSSEL,DEPT DRUG SAFETY/KANSAS CITY//MO/64137; F HOFFMANN LAROCHE,PHARMACEUT RES GENE TECHNOL, DEPT BIOL/BASEL//SWITZERLAND/
PUBLICATION TYPE: JOURNAL
PUBLICATION: JOURNAL OF IMMUNOLOGY, 1996, V157, N4 (AUG 15), P1758-1772
GENUINE ARTICLE#: VH124
PUBLISHER: AMER ASSOC IMMUNOLOGISTS, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814
ISSN: 0022-1767
LANGUAGE: English DOCUMENT TYPE: ARTICLE

ABSTRACT: We have used fas-defective MRL-lpr/lpr mice to study the effects of the staphylococcal enterotoxin superantigens on the development of autoimmune, inflammatory joint disease In animals that are susceptible to the developmentof rheumatoid arthritis-like disease. We show that systematic administration by a single i.p. injection of staphylococcal *enterotoxin"** *B"** (*SEB"**; 10 mu g/mouse) caused a mild, inflammatory arthritis +30 days postchallenge in theknee joints of young (<2-mo-old) MRL-lpr/lpr mice, but not aged-matched MRL +/+ mice, In aged (>8-mo-old) MRL-lpr/lpr mice, but not in aged MRL +/+ mice, *SEB"** caused a severe, inflammatory arthritis, as assessed histologically, and systemic autoimmune disease, including glomerulonephritis and autoantibody production. Furthermore, in aged MRL-lpr/lpr mice, *SEB"** but not heat-denatured *SEB"** caused acute weight loss and elevated levels of serum proinflammatory cytokines. Compared with highly purified peritoneal macrophages obtained from either aged MRL +/+, young MRL-lpr/lpr, or young MRL +/+, peritoneal macrophages obtained from aged MRL-lpr/lpr mice constitutively expressed 2- to 10-fold greater levels of TNF-alpha, IL-1 beta, IL-6, and IL-10, and produced elevated amounts of these cytokines when treated in vitro withSEB. *SEB"**-challenged aged MRL-lpr/lpr mice treated with anti-TNF mAb (100 mu g/mouse; every other day), anti-V beta 8 TCR mAb (250 mu g/mouse; every other day), or orally with the novel TNF-alpha inhibitor MDL 201,449A (9-[(1R, 3R)-trans-cyclopentan-3-ol]

adenine; 25 mg/kg/day) exhibited reduced inflammatory arthritis, autoantibody formation, and serum TNF-alpha levels, but not IL-10 levels, after +30 days of treatment. These data suggest that *SEB"** is an extremely potent macrophage-activating factor in vitro and in vivo, enhancing several aspects of autoimmune disease in MRL-lpr/lpr mice, and that anti-TNF *therapies"** may have potential use in inflammatory *arthritis"**.

4/3,AB/9 (Item 4 from file: 440)
DIALOG(R)File 440:Current Contents Search(R)

07365274 References: 27
TITLE: REPOPULATION OF BLOOD LYMPHOCYTE SUB-POPULATIONS IN RHEUMATOID *ARTHRITIS"** PATIENTS *TREATED"** WITH THE DEPLETING HUMANIZED MONOCLONAL ANTIBODY, CAMPATH-1H
AUTHOR(S): BRETT S; BAXTER G; COOPER H; JOHNSTON JM; TITE J; RAPSON N
CORPORATE SOURCE: GLAXO WELLCOME MED RES CTR,IMMUNOL UNIT,GUMELS WOOD RD/STEVENAGE SG1 2NY/HERTS/ENGLAND/ (Reprint); WELLCOME RES LABS,DIV BIOL,MOLEC IMMUNOL GRP/BECKENHAM BR3 3BS/KENT/ENGLAND/; BURROUGHS WELLCOME CO/RES TRIANGLE PK//NC/27709
PUBLICATION: IMMUNOLOGY, 1996, V88, N1 (MAY), P13-19
GENUINE ARTICLE#: UJ686
ISSN: 0019-2805
LANGUAGE: ENGLISH DOCUMENT TYPE: ARTICLE

ABSTRACT: Patients with severe rheumatoid *arthritis"** who had failed *treatment"** with conventional *therapies"** were *treated"** with a course of five or 10 daily intravenous infusions of CAMPATH-1H, a humanized antibody against the CD52 antigen, resulting in profound depletion of peripheral blood mononuclear cells. During the subsequent 18 months, lymphocytes were analysed for subpopulations by fluorescence-activated cell sorter (FAGS) and for proliferation in response to polyclonal T-cell stimulation with anti-CD3 or staphylococcal *enterotoxin"** *B"** (SEE). Treatment resulted in almost complete depletion of lymphocytes from the blood followed by gradual repopulation. CD16(+) natural killer (NK) cells and CD14(+) monocytes returned to pretreatment levels within 1-2 months. CD19(+) B cells returned to within 50% of pre-treatment levels by day 66 and to within normal range by day 150, whereas CD8(+) T cells recovered to 50% of pretreatment levels by day 66, but did not show any further increase during the rest of the study period. The most profound effects were on the CD4(+) T lymphocyte sub-population, as the mean CD4(+) count did not increase above 20% of pre-treatment level at any time during the study period (550 days), at all the doses tested. The T cells which initially repopulated the blood 1-2 months after treatment, nearly all expressed the activation markers human leucocyte antigen (HLA)-DR and CD45RO, although the percentage of T cells expressing these molecules gradually declined to normal levels over time. Proliferative responses to polyclonal T-cell stimulation (anti-CD3 and SEE) were also significantly reduced in the first few months after treatment, but recovered to pre-treatment levels by day 250. The relationship between these observations and the clinical response is discussed.

4/3,AB/10 (Item 5 from file: 440)
DIALOG(R)File 440:Current Contents Search(R)

05651324 References: 18
TITLE: THE MODEL OF ARTHRITIS INDUCED BY SUPERANTIGEN IN MICE
AUTHOR(S): NAGAI H; TAKAOKA Y; KAMADA H; MORI H
CORPORATE SOURCE: GIFU PHARMACEUT UNIV,DEPT PHARMACOL,5-6-1 MITAHORAHIGASHI/GIFU 502//JAPAN/ (Reprint)
PUBLICATION: LIFE SCIENCES, 1994, V55, N12, PPL233-PL237
GENUINE ARTICLE#: PB211
ISSN: 0024-3205
LANGUAGE: ENGLISH DOCUMENT TYPE: LETTER

ABSTRACT: Subcutaneous injection of *Staphylococcal"** enterotoxine B (*SEB"**) produced by *Staphylococcus"** aureus, caused severe arthritis in DBA/1J mice which had been previously immunizated with bovine type II collagen. The severity of this arthritis was dose dependent and prolonged joint inflammation with erosion of bone was observed. Anti - type II collagen antibodies were detected in the serum of arthritic mice. Effector T cells against type II collagen were also detected by means of delayed type hypersensitivity in the skin. Moreover, a significant decrease in the ratio between T cells and B cells and an increase in the ratio between CD4(+) cells and CD8(+) cells was observed in spleen cells from arthritic mice. Prednisolone supresses the induction and development of clinical signs of arthritis in mice. This evidence suggests that this experimental arthritis model may provide a means to examine the role of superantigens and the efficacy of pharmacological agents for the *treatment"** of rheumatoid *arthritis"**.

4/3,AB/11 (Item 6 from file: 440)
DIALOG(R)File 440:Current Contents Search(R)

05163525 References: 78
TITLE: T CELL INFLUENCE ON SUPERANTIGEN-INDUCED ARTHRITIS IN MRL-LPR/LPR MICE
AUTHOR(S): MOUNTZ JD; ZHOU T; LONG RE; BLUETHMANN H; KOOPMAN WJ; EDWARDS CK
CORPORATE SOURCE: UNIV ALABAMA,DEPT MED,DIV CLIN IMMUNOL & RHEUMATOL,LHR 405/BIRMINGHAM//AL/35294 (Reprint); VET AFFAIRS MED CTR/BIRMINGHAM//AL/00000; F HOFFMANN LA ROCHE & CO LTD,NEW TECHNOL,PHARMACEUT RES,DEPT BIOL/BASEL//SWITZERLAND/; MARION MERRELL DOW RES INST,DEPT TOXICOL/CINCINNATI//OH/00000; MARION MERRELL DOW RES INST,DEPT IMMUNOL/CINCINNATI//OH/00000
PUBLICATION: ARTHRITIS AND RHEUMATISM, 1994, V37, N1 (JAN), P113-124
GENUINE ARTICLE#: MR523
ISSN: 0004-3591
LANGUAGE: ENGLISH DOCUMENT TYPE: ARTICLE

ABSTRACT: Objective. To define the influence of the T cell receptor (TCR) and the lpr autoimmune gene on the induction and progression of superantigen-induced arthritis in V(beta)8 transgenic MRL-lpr/lpr mice. Methods. The time to onset and the extent of synovial hyperplasia after the induction of arthritis by intraarticular injection of staphylococcal *enterotoxin"** *B"** (*SEB"**) were compared in mice having T cells that bear the V(beta)8 transgene alone (V(beta)8 TCR transgenic MRL-+/+), the lpr gene without the V(beta)8 gene (nontransgenic MRL-lpr/lpr), both the V(beta)8 gene and the lpr gene (V(beta)8 transgenic MRL-lpr/lpr), or neither gene (nontransgenic MRL-+/+). Synovial hyperplasia was compared in SEE-injected V(beta)8 transgenic MRL-lpr/lpr mice after treatment with

cyclosporin A (CSA), anti-V(beta)8 and anti-CD4 monoclonal antibodies, and in V(beta)8 transgenic MRL-lpr/lpr mice after injection of a non-V(beta)8-reactive superantigen, *staphylococcal"** enterotoxin A (SEA). Results. At day 30, increased synovial cells were observed in all *SEB"** -treated mice, but the increase was greatest in the V(beta)8 transgenic MRL-lpr/lpr mice. T cell involvement was indicated by the inability of either heat-denatured *SEB"** or SEA to induce severe *arthritis"**, the reduction in the severity of the *arthritis"** on systemic *treatment"** with CSA or anti-V(beta)8, and the correlation of synovial hyperplasia with in vitro *SEB"** reactivity of T cells. Conclusion. These observations suggest that superantigens can induce chronic arthritis and that the induction and progression of the arthritis requires an underlying T cell defect in anergy induction in addition to exposure to the superantigen.

4/3,AB/12 (Item 7 from file: 440)
DIALOG(R)File 440:Current Contents Search(R)

04230492 References: 48
TITLE: BACTERIAL AGENTS PROTECT AGAINST AUTOIMMUNE DISEASE .1. MICE PRE-EXPOSED TO BORDETELLA-PERTUSSIS OR MYCOBACTERIUM-TUBERCULOSIS ARE HIGHLY REFRACTORY TO INDUCTION OF EXPERIMENTAL AUTOIMMUNE ENCEPHALOMYELITIS
AUTHOR(S): LEHMANN D; BENNUN A (Reprint)
CORPORATE SOURCE: WEIZMANN INST SCI,DEPT CELL BIOL/IL-76100 REHOVOT//ISRAEL/ (Reprint); WEIZMANN INST SCI,DEPT CELL BIOL/IL-76100 REHOVOT//ISRAEL/
PUBLICATION: JOURNAL OF AUTOIMMUNITY, 1992, V5, N6 (DEC), P675-690
GENUINE ARTICLE#: KE488
ISSN: 0896-8411
LANGUAGE: ENGLISH DOCUMENT TYPE: ARTICLE

4/3,AB/13 (Item 1 from file: 348)
DIALOG(R)File 348:EUROPEAN PATENTS

01552168
Methods and materials for preparation of modified antibody variable domains and therapeutic uses thereof
Verfahren und Materialien zur Herstellung von modifizierten Antikorper Variablen Domanen und deren therapeutischen Verwendung
Procedes et matieres de preparation de domaines variables d'anticorps modifies et leurs utilisations therapeutiques
PATENT ASSIGNEE:
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PATENT (CC, No, Kind, Date): EP 1291360 A1 030312 (Basic)
APPLICATION (CC, No, Date): EP 2002021775 921214;

PRIORITY (CC, No, Date): US 808464 911213
DESIGNATED STATES: AT; BE; CH; DE; DK; ES; FR; GB; GR; IE; IT; LI; LU; MC; NL; PT; SE
RELATED PARENT NUMBER(S) - PN (AN):
EP 571613 (EP 93901238)
INTERNATIONAL PATENT CLASS: C07K-016/28; C07K-016/46

ABSTRACT EP 1291360 A1
Methods are described for identifying the amino acid residues of an antibody variable domain which may be modified without diminishing the native affinity of the domain for antigen while reducing its immunogenicity with respect to a heterologous species and for preparing so modified antibody variable domains which are useful for administration to heterologous species. Antibody variable regions prepared by the methods of the invention are also described.
ABSTRACT WORD COUNT: 68
NOTE:
Figure number on first page: 3

LANGUAGE (Publication,Procedural,Application): English; English; English
FULLTEXT AVAILABILITY:

Available Text	Language	Update	Word Count
CLAIMS A	(English)	200311	1272
SPEC A	(English)	200311	16550
Total word count - document A			17822
Total word count - document B			0
Total word count - documents A + B			17822

4/3,AB/14 (Item 2 from file: 348)
DIALOG(R)File 348:EUROPEAN PATENTS

01510319
Methods and compositions for determining cellular response profiles
Verfahren und Zusammensetzungen zur Bestemmung von zellularen Response-Profile
Procedes et compositions pour determiner les profils de reaction cellulaire
PATENT ASSIGNEE:
Aurora Biosciences Corporation, (2370590), 11149 North Torrey Pines Road, La Jolla, CA 92037, (US), (Applicant designated States: all)
INVENTOR:
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Craig, Frank, 409 Santa Helena, Solana Beach, CA 92075, (US)
Mere, Lora, 3522 Syracuse Avenue, San Diego, CA 92122, (US)
Foulkes, Gorden J., 1220 Rancho Encinitas Drive, Encinitas, CA 92024, (US)
LEGAL REPRESENTATIVE:
Grund, Martin, Dr. et al (90761), Dr. Volker Vossius, Patentanwaltskanzlei, Geibelstrasse 6, 81679 Munchen, (DE)
PATENT (CC, No, Kind, Date): EP 1262478 A2 021204 (Basic)
EP 1262478 A3 030326
APPLICATION (CC, No, Date): EP 2002010958 970926;
PRIORITY (CC, No, Date): US 719697 960926
DESIGNATED STATES: AT; BE; CH; DE; DK; ES; FI; FR; GB; GR; IE; IT; LI; LU; MC; NL; PT; SE
RELATED PARENT NUMBER(S) - PN (AN):

EP 952976 (EP 97943625)
INTERNATIONAL PATENT CLASS: C12Q-001/00; G01N-033/50

ABSTRACT EP 1262478 A2
The invention provides methods for determining a cellular response profile for a target or chemical, for screening compounds for activity as an activator or inhibitor of a target and for developing a cell sensor panel. Furthermore, cell sensor panels are provided. Generally, the methods comprise inserting a BL (beta-lactamase) expression construct via a viral vector into an non-yeast eukaryotic genome, contained in at least one living cell, contacting the cell with a predetermined concentration of a modulator, and detecting BL activity in the cell.
ABSTRACT WORD COUNT: 85
NOTE:
Figure number on first page: NONE

LANGUAGE (Publication,Procedural,Application): English; English; English
FULLTEXT AVAILABILITY:

Available Text	Language	Update	Word Count
CLAIMS A	(English)	200249	1043
SPEC A	(English)	200249	23201
Total word count - document A			24244
Total word count - document B			0
Total word count - documents A + B			24244

4/3,AB/15 (Item 3 from file: 348)
DIALOG(R)File 348:EUROPEAN PATENTS

01443101
Nicotinamide derivatives and their mimetics as inhibitors of PDE4 isozymes
Nikotinsaureamid-Derivate und ihre Mimetika als Inhibitoren von PDE4-Isozyms
Derives du nicotinamide et leur mimetiques actifs comme ihibiteurs de PDE4 isozymes
PATENT ASSIGNEE:
Pfizer Products Inc., (2434221), Eastern Point Road, Groton, Connecticut 06340, (US), (Applicant designated States: all)
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Marfat, Anthony, Pfizer Global Research and D., Eastern Point Road, Groton, Connecticut 06340, (US)
LEGAL REPRESENTATIVE:
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PATENT (CC, No, Kind, Date): EP 1229034 A1 020807 (Basic)
APPLICATION (CC, No, Date): EP 2002250202 020111;
PRIORITY (CC, No, Date): US 265240 P 010131
DESIGNATED STATES: AT; BE; CH; CY; DE; DK; ES; FI; FR; GB; GR; IE; IT; LI; LU; MC; NL; PT; SE; TR
EXTENDED DESIGNATED STATES: AL; LT; LV; MK; RO; SI
INTERNATIONAL PATENT CLASS: C07D-401/12; C07D-405/12; C07D-405/14; C07D-413/12; C07D-213/64; A61K-031/44; A61K-031/455; A61P-029/00; A61P-037/08; A61P-011/06

ABSTRACT EP 1229034 A1

Compounds useful as inhibitors of PDE4 in the treatment of diseases regulated by the activation and degranulation of eosinophils, especially asthma, chronic bronchitis, and chronic obstructive pulmonary disease, of the formula: wherein j is 0 or 1, k is 0 or 1, m is 0, 1, or 2; n is 1 or 2; A is is selected from the partial Formulas: where q is 1, 2, or 3, W3) is -O-; -N(R9))-; or -OC(=O)-; R7) is selected from -H; -(C1))-C6)))alkyl, -(C2))-C6)))alkenyl, or -(C2))-C6)))alkynyl substituted by 0 to 3 substituents R10); -(CH2)))u))-(C3))-C7))) cycloalkyl where u is 0, 1 or 2, substituted by 0 to 3 R10); and phenyl or benzyl substituted by 0 to 3 R14); R8) is tetrazol-5-yl; 1,2,4-triazol-3-yl; 1,2,4-triazol-3-on-5-yl; 1,2,3-triazol-5-yl; imidazol-2-yl; imidazol-4-yl; imidazolidin-2-on-4-yl; 1,3,4-oxadiazolyl; 1,3,4-oxadiazol-2-on-5-yl; 1,2,4-oxadiazol-3-yl; 1,2,4-oxadiazol-5-on-3-yl; 1,2,4-oxadiazol-5-yl; 1,2,4-oxadiazol-3-on-5-yl; 1,2,5-thiadiazolyl; 1,3,4-thiadiazolyl; morpholinyl; parathiazinyl; oxazolyl; isoxazolyl; thiazolyl; isothiazolyl; pyrrolyl; pyrazolyl; succinimidyl; glutarimidyl; pyrrolidonyl; 2-piperidonyl; 2-pyridonyl; 4-pyridonyl; pyridazin-3-onyl; pyridyl; pyrimidinyl; pyrazinyl; pyridazinyl; indolyl; indolinyl; isoindolinyl; benzo(b)furanyl; 2,3-dihydrobenzofuranyl; 1,3-dihydroisobenzofuranyl; 2H-1-benzopyranyl; 2-H-chromenyl; chromanyl; benzothienyl; 1H-indazolyl; benzimidazolyl; benzoxazolyl; benzisoxazolyl; benzothiazolyl; benzotriazolyl; benzotriazinyl; phthalazinyl; 1,8-naphthyridinyl; quinolinyl; isoquinolinyl; quinazolinyl; quinoxalinyl; pyrazolo(3,4-d)pyrimidinyl; pyrimido(4,5-d)pyrimidinyl; imidazo(1,2-a)pyridinyl; pyridopyridinyl; pteridinyl; or 1H-purinyl; or A is selected from phosphorous and sulfur acid groups; W is (horizontal bar)O(horizontal bar); (horizontal bar)S(=O)t))(horizontal bar), where t is 0, 1, or 2; or -N(R3))(horizontal bar); Y is C(R1)a)))(horizontal bar), or -(N(square)(O)k))) where k is 0 or 1; R4), R5) and R6) are (1)(horizontal bar)H; provided that R5) and R6) are not both -H at the same time, (horizontal bar)F; (horizontal bar)Cl; -(C2))-C4))) alkynyl; -R16); (horizontal bar)OR16); -S(=O)p))R16); (horizontal bar)C(=O)R16), -C(=O)OR16); -OC(=O)R16); -CN; -NO2)); -C(=O)NR16)R17); -OC(=O)NR16)R17); (horizontal bar)NR12)a))C(=O)NR16)R17); -NR12)a))C(=NR12))NR16)R17); -NR12)a))C(=NCN)NR15)R16); -NR12)a))C(=N-NO2)))NR15)R16); -C(=NR12)a)))NR15)R16); -CH2))C(=NR12)a)))NR16)R17); (horizontal bar)OC(=NR12)a)))NR16)R17); (horizontal bar)OC(=N(horizontal bar)NO2)))NR16)R17); -NR16)R17); -CH2))NR16)R17); -NR12)a))C(=O)R16); -NR12)a))C(=O)OR16); =NOR16); (horizontal bar)NR12)a))S(=O)p))R17) -S(=O)p))NR16)R17); and (horizontal bar)CH2))C(=NR12)a)))NR16)R17); (2) -(C1))-C4))) alkyl including dimethyl and -(C1))-C4))) alkoxy substituted with 0 to 3 substituents (horizontal bar)F or (horizontal bar)Cl; or 0 or 1 substituent (C1))-C2))) alkoxycarbonyl(horizontal bar), (C1))-C2))) alkylcarbonyl(horizontal bar), or (C1))-C2))) alkylcarbonyloxy(horizontal bar); or (3) an aryl or heterocyclic moiety; or (4) R5) and R6) are taken together to form a moiety of partial Formulas (1.3.1) through (1.3.15): B1) and B2) is a moiety comprising a saturated or unsaturated carbon ring system that is 3- to 7-membered monocyclic, or that is 7- to 12-membered, fused or discontinuous, polycyclic; wherein optionally one carbon atom thereof may be replaced by a heteroatom selected from N, O and S; and where N is selected, optionally a second carbon atom thereof may be replaced by a heteroatom selected from N, O, or S;

or a pharmaceutically acceptable salt thereof.

ABSTRACT WORD COUNT: 420

LANGUAGE (Publication,Procedural,Application): English; English; English
FULLTEXT AVAILABILITY:

Available Text	Language	Update	Word Count
CLAIMS A	(English)	200232	4124
SPEC A	(English)	200232	53926
Total word count - document A			58050
Total word count - document B			0
Total word count - documents A + B			58050

4/3,AB/16 (Item 4 from file: 348)
DIALOG(R)File 348:EUROPEAN PATENTS

01093291
Peptide T and related peptides in the treatment of inflammation, including multiple sclerosis
T-peptid und damit verwandte Peptide in der Behandlung von entzundungen einschlies slich der Multiplen Sklerose
Peptide T et peptides associes destines au traitement des inflammations, notamment la sclerose en plaques
PATENT ASSIGNEE:
PEPTECH LIMITED, (1058961), 35-41 Waterloo Road, North Ryde, New South Wales 2113, (AU), (Applicant designated States: all)
DRUG ROYALTY CORPORATION, (1710570), 8 King Street East, Suite 202, Toronto, Ontario M5c 1B5, (CA), (Applicant designated States: all)
INVENTOR:
Andersen, Anders Jorgen, Havrevaegnet 331, 2980 Kokkedal, (DK)
Aston, Roger, Norbach House, Charterhouse-on-Mendip, Blagdon, Bristol BS40 7XW, (GB)
Carlen, Peter Louis, 529 St. Clements Avenue, Toronto, Ontario M5N 1M3, (CA)
Doob, Penelope Reed, 1 Fenwick Avenue, Toronto, Ontario M4J 3HZ, (CA)
Phipps, David James, 81 Pauline Avenue, Apt. 1, Toronto, Ontario M5H 3M7, (CA)
MacFadden, Douglas Kevin, 228 Chatham Avenue, Toronto, Ontario M4J 1KG, (CA)
Rathjen, Deborah, 4 Eddy Street, Thornleigh, NSW 2120, (AU)
Widmer, Fred, 35 Anzac Avenue, Ryde, NSW 2112, (AU)
LEGAL REPRESENTATIVE:
Woods, Geoffrey Corlett (48721), J.A. KEMP & CO. Gray's Inn 14 South Square, London WC1R 5LX, (GB)
PATENT (CC, No, Kind, Date): EP 960886 A1 991201 (Basic)
APPLICATION (CC, No, Date): EP 99101349 930329;
PRIORITY (CC, No, Date): US 858832 920327; DK 92645 920514; US 915118 920717; US 987674 921209
DESIGNATED STATES: AT; BE; CH; DE; DK; ES; FR; GB; GR; IE; IT; LI; LU; MC; NL; PT; SE
RELATED PARENT NUMBER(S) - PN (AN):
EP 635027 (EP 93907942)
INTERNATIONAL PATENT CLASS: C07K-005/10; C07K-014/00; A61K-038/08

ABSTRACT EP 960886 A1
Peptide T and its linear or cyclic analogues of the General Formula 1:
wherein
A is Ala, Gly, Val, Ser, Thr or absent;
B is Ala, Gly, Val, Ser, Thr or absent;
C is Ser, Thr or absent;

D is Ser, Thr, Asn, Glu, Arg, Ile, Leu or absent;
E is Ser, Thr, Asp or absent;
F is Thr, Ser, Asn, Arg, Gln, Lys, Trp or absent;
G is Tyr or absent;
H is Thr, Arg, Gly, Met, Met(O), Cys, Thr, Gly or absent;

and
I is Cys or absent;
II is Cys, an amide group, substituted amide group, an ester group or absent; at least one of the amino acids optionally being substituted by a monomeric or polymeric carbohydrate or derivative thereof, such substitution being accomplished through hydroxyl and/or amino and/or amido groups of the amino acids, comprising at least 4 amino acids, and their pharmaceutically acceptable salts, are useful in the treatment or prevention of inflammation. In particular, the peptides are useful in the treatment or prevention of multiple sclerosis, myelopathies (including HTLV-1 associate myelopathy) and symptoms and diseases associated with chronic immune activation, including chronic fatigue syndrome, toxic shock, arthritis, inflammatory bowel disease and host-versus-graft and graft-versus-host responses in transplant recipients.
ABSTRACT WORD COUNT: 216
NOTE:
Figure number on first page: NONE

LANGUAGE (Publication,Procedural,Application): English; English; English
FULLTEXT AVAILABILITY:

Available Text	Language	Update	Word Count
CLAIMS A	(English)	9948	362
SPEC A	(English)	9948	16432
Total word count - document A			16794
Total word count - document B			0
Total word count - documents A + B			16794

4/3,AB/17 (Item 5 from file: 348)
DIALOG(R)File 348:EUROPEAN PATENTS

01085562
NOVEL *PREVENTIVES"**/*REMEDIES"** FOR *IMMUNOPATHY"**
NEUE VORBEUGUNGSMEDIZIN/HEILMITTEL FUR IMMUNOPATHIEN
NOUVEAUX MEDICAMENTS *PREVENTIFS"**/CURATIFS DE L'*IMMUNOPATHIE"**
PATENT ASSIGNEE:
Juridical Foundation, The Chemo-Sero-Therapeutic Research Institute, (283933), 6-1, Okubo 1-chome, Kumamoto-shi, Kumamoto 860-8568, (JP), (Applicant designated States: all)
KOWA COMPANY LTD., (410437), 6-29, Nishiki 3-chome, Naka-ku, Nagoya-shi, Aichi-ken 460-0003, (JP), (Applicant designated States: all)
INVENTOR:
SASAKI, Takumi, 301-72, Ishihara-machi, Kumamoto-shi, Kumamoto 862-8014, (JP)
KIMACHI, Kazuhiko, 908-121, Yuge, Tatsuda-machi, Kumamoto-shi, Kumamoto 862-8002, (JP)
SOEJIMA, Kenji, Koyosokushinjutaku 1-407,1254-4Kamitatsuda,Tatsuda, Kumamoto-shi, Kumamoto 862-8004, (JP)
KIMURA, Yumi, Okawa-haitsu 201, 3020, Tsukure, Kikuyo-machi, Kikuchi, Kumamoto 869-1101, (JP)
NOZAKI, Chikateru, 26-1, Musashigaoka 5-chome, Kumamoto-shi, Kumamoto

862-8001, (JP)
FUJIYAMA, Yoshihide, 41-22, Nango 2-chome, Otsu-shi, Shiga 520-0865, (JP)
LEGAL REPRESENTATIVE:
Jaenichen, Hans-Rainer, Dr. et al (59061), Vossius & Partner, Postfach 86 07 67, 81634 Munchen, (DE)
PATENT (CC, No, Kind, Date): EP 1055429 A1 001129 (Basic)
WO 9940935 990819
APPLICATION (CC, No, Date): EP 99902905 990215; WO 99JP638 990215
PRIORITY (CC, No, Date): JP 9850137 980215
DESIGNATED STATES: AT; BE; CH; CY; DE; DK; ES; FI; FR; GB; GR; IE; IT; LI; LU; MC; NL; PT; SE
INTERNATIONAL PATENT CLASS: A61K-039/09; A61K-038/16; C12N-015/09; C07K-14:315

ABSTRACT EP 1055429 A1
A prophylactic/*remedy"** for *immunopathy"** for *immunopathy"** comprising, as an active ingredient, modifications of *Staphylococcal"** *enterotoxin"** *B"** (*SEB"**) with substitution of at least one amino acid residues within the amino acid sequence of natural type *SEB"**, or derivatives thereof, wherein said *SEB"** modifications or derivatives thereof have inhibitory activity on T cell activation wherein they interact with specific V(beta) component of T cell receptor (TCR) but are reduced in their immunological responsiveness to *SEB"** without inducing elimination of T cells having specific V(beta) component, the elimination being normally induced by natural type *SEB"** or recombinant wild-type *SEB"**.
ABSTRACT WORD COUNT: 97
NOTE:
Figure number on first page: NONE

LANGUAGE (Publication,Procedural,Application): English; English; Japanese
FULLTEXT AVAILABILITY:

Available Text	Language	Update	Word Count
CLAIMS A	(English)	200048	527
SPEC A	(English)	200048	5949
Total word count - document A			6476
Total word count - document B			0
Total word count - documents A + B			6476

4/3,AB/18 (Item 6 from file: 348)
DIALOG(R)File 348:EUROPEAN PATENTS

01040748
USE OF 6, 7-SUBSTITUTED 2-AMINOTETRALINES FOR THE TREATMENT OF CYTOKINE MEDIATED INFLAMMATORY CONDITIONS
VERWENDUNG VON 6,7-SUBSTITUIERTER 2-AMINOTETRALINE ZUR BEHANDLUNG VON ZYTOKIN-VERMITTLETEN ENTZUNDUNGSZUSTANDEN
UTILISATION DE 2-AMINOTETRALINES 6,7-SUBSTITUEES POUR LA PREPARATION DE COMPOSITIONS PHARMACEUTIQUES POUR LE TRAITEMENT DE PATHOLOGIES INFLAMMATOIRES ET/OU AUTO-IMMUNES
PATENT ASSIGNEE:
SIGMA-TAU Industrie Farmaceutiche Riunite S.p.A., (255110), Viale Shakespeare, 47, 00144 Roma, (IT), (Proprietor designated states: all)
INVENTOR:
FORESTA, Piero, Via L. Sturzo, 46, I-00040 Pomezia, (IT)
RUGGIERO, Vito, Via Lugnano in Teverina, 32, I-00181 Rome, (IT)

LEGAL REPRESENTATIVE:
Spadaro, Marco et al (83513), Sigma-Tau Industrie Farmaceutiche Riunite SpA, 47,Viale Shakespeare, 00144 Rome, (IT)
PATENT (CC, No, Kind, Date): EP 1017377 A2 000712 (Basic)
EP 1017377 B1 011205
WO 9915160 990401
APPLICATION (CC, No, Date): EP 98946704 980918; WO 98IT250 980918
PRIORITY (CC, No, Date): IT 97RM569 970922
DESIGNATED STATES: AT; BE; CH; DE; DK; ES; FI; FR; GB; GR; IE; IT; LI; LU; MC; NL; PT; SE
EXTENDED DESIGNATED STATES: AL; LT; LV; MK; RO; SI
INTERNATIONAL PATENT CLASS: A61K-031/135
NOTE:
No A-document published by EPO
LANGUAGE (Publication,Procedural,Application): English; English; English
FULLTEXT AVAILABILITY:

Available Text	Language	Update	Word Count
CLAIMS B	(English)	200149	180
CLAIMS B	(German)	200149	169
CLAIMS B	(French)	200149	208
SPEC B	(English)	200149	3508
Total word count - document A			0
Total word count - document B			4065
Total word count - documents A + B			4065

4/3,AB/19 (Item 7 from file: 348)
DIALOG(R)File 348:EUROPEAN PATENTS

00943464
METHODS AND COMPOSITIONS FOR SENSITIVE AND RAPID, FUNCTIONAL IDENTIFICATION OF GENOMIC POLYNUCLEOTIDES AND USE FOR CELLULAR ASSAYS IN DRUG DISCOVERY
METHODEN UND ZUSAMMENSETZUNGEN ZUR EMPFINDLICHEN UND SCHNELLEN FUNKTIONELLEN IDENTIFIZIERUNG GENOMISCHER POLYNUKLEOTIDE UND IHRE ANWENDUNG IN ZELLTESTS ZUM AUFFINDEN VON MEDIKAMENTEN
PROCEDES ET COMPOSITIONS POUR L'IDENTIFICATION SENSIBLE, RAPIDE ET FONCTIONNELLE DE POLYNUCLEOTIDES GENOMIQUES, ET LEUR UTILISATION POUR L'ANALYSE CELLULAIRE DANS LA MISE AU POINT DE MEDICAMENTS
PATENT ASSIGNEE:
Aurora Biosciences Corporation, (2370590), 11149 North Torrey Pines Road, La Jolla, CA 92037, (US), (Proprietor designated states: all)
INVENTOR:
WHITNEY, Michael, A., 8320 Via Sonoma 81, La Jolla, CA 92037, (US)
NEGULESCU, Paul, A., 678 Solana Circle, Solana Beach, CA 92075, (US)
CRAIG, Frank, 409 Santa Helena, Solana Beach, CA 92075, (US)
MERE, Lora, 3522 Syracuse Avenue, San Diego, CA 92122, (US)
FOULKES, Gorden, J., 1220 Rancho Encinitas Drive, Encinitas, CA 92024, (US)
LEGAL REPRESENTATIVE:
Vossius, Volker, Dr. et al (12524), Dr. Volker Vossius, Patentanwaltskanzlei - Rechtsanwaltskanzlei, Geibelstrasse 6, 81679 Munchen, (DE)
PATENT (CC, No, Kind, Date): EP 952976 A1 991103 (Basic)
EP 952976 B1 021211
WO 98013353 980402
APPLICATION (CC, No, Date): EP 97943625 970926; WO 97US17395 970926

PRIORITY (CC, No, Date): US 719697 960926
DESIGNATED STATES: AT; BE; CH; DE; DK; ES; FI; FR; GB; GR; IE; IT; LI; LU; MC; NL; PT; SE
RELATED DIVISIONAL NUMBER(S) - PN (AN):
EP 1262478 (EP 2002010958)
INTERNATIONAL PATENT CLASS: C07D-221/02; C07D-215/12; C12Q-001/70; C12Q-001/68; C12Q-001/08; C12P-021/06; C12N-015/00; C12N-009/14; C12N-009/84; C12N-009/86; C12Q-001/00; G01N-033/50
NOTE:
No A-document published by EPO
LANGUAGE (Publication,Procedural,Application): English; English; English
FULLTEXT AVAILABILITY:

Available Text	Language	Update	Word Count
CLAIMS B	(English)	200250	713
CLAIMS B	(German)	200250	718
CLAIMS B	(French)	200250	891
SPEC B	(English)	200250	23296
Total word count - document A			0
Total word count - document B			25618
Total word count - documents A + B			25618

4/3,AB/20 (Item 8 from file: 348)
DIALOG(R)File 348:EUROPEAN PATENTS

00805514
MEDICAMENTS FOR TREATMENT OF AUTOIMMUNE DISEASES USING INTERFERON-TAU
MEDIKAMENTE ZUR BEHANDLUNG VON AUTOIMMUNERKRANKUNGEN MIT INTERFERON-TAU
MEDICAMENTS POUR LE TRAITEMENT DE MALADIES AUTO-IMMUNES A L'AIDE DE L'INTERFERON TAU
PATENT ASSIGNEE:
UNIVERSITY OF FLORIDA, (429779), 223 Grinter Hall, Division of Sponsored Research P.O. Box 115500, Gainesville, Florida 32611-5500, (US), (Proprietor designated states: all)
INVENTOR:
SOOS, Jeanne M., Apartment 236, 507 N.W. 39th Road, Gainesville, FL 32607, (US)
SCHIFFENBAUER, Joel, 368 N.W. 48th Boulevard, Gainesville, FL 32607, (US)
JOHNSON, Howard, Marcellus, 4404 N.W. 75th Street, Gainesville, FL 32606, (US)
LEGAL REPRESENTATIVE:
VOSSIUS & PARTNER (100311), Postfach 86 07 67, 81634 Munchen, (DE)
PATENT (CC, No, Kind, Date): EP 814831 A1 980107 (Basic)
EP 814831 B1 020619
WO 9628183 960919
APPLICATION (CC, No, Date): EP 96911300 960315; WO 96US3472 960315
PRIORITY (CC, No, Date): US 406190 950316
DESIGNATED STATES: AT; BE; CH; DE; DK; ES; FI; FR; GB; GR; IE; IT; LI; LU; MC; NL; PT; SE
INTERNATIONAL PATENT CLASS: A61K-038/21; C07K-014/555; C12N-015/20
NOTE:
No A-document published by EPO
LANGUAGE (Publication,Procedural,Application): English; English; English
FULLTEXT AVAILABILITY:

Available Text	Language	Update	Word Count
CLAIMS B	(English)	200225	238
CLAIMS B	(German)	200225	216

CLAIMS B	(French)	200225	242
SPEC B	(English)	200225	15012
Total word count - document A			0
Total word count - document B			15708
Total word count - documents A + B			15708

4/3,AB/21 (Item 9 from file: 348)
DIALOG(R)File 348:EUROPEAN PATENTS

00622498
THERAPEUTIC INHIBITOR OF VASCULAR SMOOTH MUSCLE CELLS
THERAPEUTISCHER INHIBITOR DER VASKULAREN GLATTEN MUSKELZELLEN
INHIBITEUR THERAPEUTIQUE DE CELLULES DES MUSCLES VASCULAIRES LISSES
PATENT ASSIGNEE:
NEORX CORPORATION, (727931), 410 West Harrison Street, Seattle Washington 98119, (US), (Proprietor designated states: all)
INVENTOR:
KUNZ, Lawrence Leroy, 1822 235th Place, Norheast, Redmond, WA 98053, (US)
LEGAL REPRESENTATIVE:
Dzieglewska, Hanna Eva et al (73231), Frank B. Dehn & Co., European Patent Attorneys, 179 Queen Victoria Street, London EC4V 4EL, (GB)
PATENT (CC, No, Kind, Date): EP 752885 A1 970115 (Basic)
EP 752885 B1 030709
WO 94007529 940414
APPLICATION (CC, No, Date): EP 94911762 920925; WO 92US8220 920925
PRIORITY (CC, No, Date): EP 94911762 920925; WO 92US8220 920925
DESIGNATED STATES: AT; BE; CH; DE; DK; ES; FR; GB; GR; IE; IT; LI; LU; MC; NL; SE
RELATED DIVISIONAL NUMBER(S) - PN (AN):
(EP 2003015404)
INTERNATIONAL PATENT CLASS: A61K-039/00; A61K-047/48
NOTE:
No A-document published by EPO
Figure number on first page: NONE
LANGUAGE (Publication,Procedural,Application): English; English; English
FULLTEXT AVAILABILITY:

Available Text	Language	Update	Word Count
CLAIMS B	(English)	200328	566
CLAIMS B	(German)	200328	497
CLAIMS B	(French)	200328	610
SPEC B	(English)	200328	21653
Total word count - document A			0
Total word count - document B			23326
Total word count - documents A + B			23326

4/3,AB/22 (Item 10 from file: 348)
DIALOG(R)File 348:EUROPEAN PATENTS

00452302
PHARMACEUTICAL COMPOSITION THAT MAKES CELLS EXPRESSING MHC CLASS II ANTIGENS TARGETS FOR CYTOTOXIC T-CELLS.
PHARMAZEUTISCHE ZUSAMMENSETZUNG DIE ZELLEN, WELCHE MHC-KLASSE-II-ANTIGENE EXPRIMIEREN, ZU ZIELZELLEN FUR CYTOTOXISCHE T-ZELLEN MACHT.
COMPOSITION PHARMACEUTIQUE FAISANT DE CELLULES EXPRIMANT DES ANTIGENES DE

LA CLASSE II DU COMPLEXE MAJEUR D'HISTOCOMPATIBILITE, DES CIBLES POUR LES LYMPHOCYTES
PATENT ASSIGNEE:
Pharmacia AB (reg.number 556131-9608), (1720682), , S-171 97 Stockholm, (SE), (applicant designated states: AT;BE;CH;DE;DK;ES;FR;GB;IT;LI;LU;NL;SE)
INVENTOR:
KALLAND, Terje, Odlarevgaen 31, S-240 21 Loddekopinge, (SE)
HEDLUNG, Gunnar, Martenstorget 10 C, S-223 51 Lund, (SE)
DOHLSTEN, Mikael, Lilla Sodergatan 6, S-223 53 Lund, (SE)
LANDO, Peter, Sofielundsvagen 44, S-214 34 Malmo, (SE)
LEGAL REPRESENTATIVE:
Woods, Geoffrey Corlett et al (48721), J.A. KEMP & CO. 14 South Square Gray's Inn, London WC1R 5LX, (GB)
PATENT (CC, No, Kind, Date): EP 444186 A1 910904 (Basic)
EP 444186 B1 951115
WO 9104053 910404
APPLICATION (CC, No, Date): EP 90914564 900914; WO 90SE592 900914
PRIORITY (CC, No, Date): SE 893100 890920
DESIGNATED STATES: AT; BE; CH; DE; DK; ES; FR; GB; IT; LI; LU; NL; SE
INTERNATIONAL PATENT CLASS: A61K-039/39; A61K-035/74;
NOTE:
No A-document published by EPO
LANGUAGE (Publication,Procedural,Application): English; English; English
FULLTEXT AVAILABILITY:

Available Text	Language	Update	Word Count
CLAIMS B	(English)	EPAB95	135
CLAIMS B	(German)	EPAB95	135
CLAIMS B	(French)	EPAB95	133
SPEC B	(English)	EPAB95	2211
Total word count - document A			0
Total word count - document B			2614
Total word count - documents A + B			2614

4/3,AB/23 (Item 11 from file: 348)
DIALOG(R)File 348:EUROPEAN PATENTS

00448819
ENCAPSULATION PROCESS
EINKAPSELUNGSVERFAHREN
PROCEDE D'ENCAPSULATION
PATENT ASSIGNEE:
Southern Research Institute, (225410), 2000 Ninth Avenue South, Birmingham Alabama 35205, (US), (applicant designated states: AT;BE;CH;DE;DK;ES;FR;GB;IT;LI;LU;NL;SE)
INVENTOR:
TICE, Thomas, R., 1915 Forest River Court, Birmingham, AL 35244, (US)
GILLEY, Richard, M., 4020 Royal Oak Circle, Birmingham, AL 35120, (US)
LEGAL REPRESENTATIVE:
Leissler-Gerstl, Gabriele (55115), Eisenfuhr, Speiser & Partner, Patentanwalte, Arnulfstrasse 25, 80335 Munchen, (DE)
PATENT (CC, No, Kind, Date): EP 471036 A1 920219 (Basic)
EP 471036 A1 920318
EP 471036 B1 960117
WO 9013361 901115
APPLICATION (CC, No, Date): EP 90908830 900502; WO 90US2439 900502

PRIORITY (CC, No, Date): US 347476 890504
DESIGNATED STATES: AT; BE; CH; DE; DK; ES; FR; GB; IT; LI; LU; NL; SE
INTERNATIONAL PATENT CLASS: B01J-013/12; A61K-009/58; A61K-009/52;
NOTE:
No A-document published by EPO
LANGUAGE (Publication,Procedural,Application): English; English; English
FULLTEXT AVAILABILITY:

Available Text	Language	Update	Word Count
CLAIMS B	(English)	EPAB96	1294
CLAIMS B	(German)	EPAB96	1248
CLAIMS B	(French)	EPAB96	1404
SPEC B	(English)	EPAB96	5378
Total word count - document A			0
Total word count - document B			9324
Total word count - documents A + B			9324

4/3,AB/24 (Item 1 from file: 357)
DIALOG(R)File 357:Derwent Biotech Res.

0317194 DBR Accession No.: 2003-18334 PATENT
Producing recombinant bacterial superantigens useful as a biodefense vaccines and for treating sepsis or toxic shock, by culturing Escherichia coli cells of Master Cell Bank comprising the bacterial gene - recombinant protein production via plasmid expression in host cell for use in disease therapy
AUTHOR: COFFMAN J D; GIARDINA S L; ZHU J
PATENT ASSIGNEE: US DEPT HEALTH and HUMAN SERVICES 2003
PATENT NUMBER: WO 200331471 PATENT DATE: 20030417 WPI ACCESSION NO.: 2003-468195 (200344)
PRIORITY APPLIC. NO.: US 328017 APPLIC. DATE: 20011009
NATIONAL APPLIC. NO.: WO 2002US31114 APPLIC. DATE: 20020927
LANGUAGE: English
ABSTRACT: DERWENT ABSTRACT: NOVELTY - Bacterial fermentation (M1) for producing a recombinant bacterial superantigen (SAg), involves culturing Escherichia coli cells of Master Cell Bank containing a construct comprising a recombinant bacterial SAg gene in a seed medium to yield a seed culture, culturing the cells to yield a production culture, inducing protein expression, disrupting the cells to yield a lysate, and recovering SAg protein from the lysate. DETAILED DESCRIPTION - Bacterial fermentation (M1) for producing a recombinant bacterial superantigen (SAg), involves: (1) culturing E. coli cells of Master Cell Bank containing an expression construct comprising a recombinant bacterial SAg gene operably linked to one or more expression control elements to direct expression of a recombinant SAg protein following induction in a sterile seed medium to yield a seed culture; (2) culturing the recombinant E. coli cells from the seed culture in a sterile production medium to yield a production culture; (3) inducing the recombinant E. coli cells of the production culture to express the recombinant SAg protein; (4) disrupting the recombinant E. coli cells from the production culture to yield a lysate containing the recombinant SAg protein; and (5) recovering the recombinant SAg from the lysate, where at least 50-60% of the recombinant SAg is recovered in a soluble form. INDEPENDENT CLAIMS are also included for: (1) high yield purification (M2) of a substantially purified SAg suitable for administration to a mammal, comprises: (1) contacting a starting load material comprising the recombinant SAg and one or more contaminants to

a hydrophobic interaction chromatography (HIC) substrate and washing to HIC substrate; (2) collecting a flow through fraction from the HIC wash, the flow through fraction comprising HIC-purified recombinant SAg partially or completely separated from the contaminants; (3) subjecting the HIC-purified recombinant SAg to a suitable buffer exchange to desalt the HIC- purified SAg fractions; (4) subjecting the HIC-purified recombinant SAg following the buffer exchange to a cation exchange chromatography substrate under conditions sufficient to bind the recombinant SAg to the cation exchange substrate, while not substantially binding the contaminants; and (5) eluting the recombinant SAg from the cation exchange substrate to provide a high yield substantially purified SAg protein suitable for administration to a mammalian subject; and (2) a recombinant SAg composition produced by (M2). BIOTECHNOLOGY - Preferred Method: In (M1), greater than 60%, 75-80%, 90% or more of the recombinant SAg is recovered in a soluble form. (M2) Comprises culturing the recombinant E. coli cells of the seed culture in sterile seed medium of form a second seed culture, and culturing the recombinant E. coli cells of the second seed culture in sterile production medium to from the production culture. The lysate is substantially free of SAg in an aggregate form as determined by the presence of inclusion bodies. The seed medium is a yeast extract-based culture medium. The seed medium comprises one or more of a trace element comprising NH4SO4, ZnSO4.7H2O, CuSO4.5H2O, MnSO4.H2O, FeCl3.6H2O, CoCl2.6H2O, or Na2MoO4.2H2O. The seed medium excludes added glucose and animal nitrogen sources, and comprises tryptone or soytone as a non-animal nitrogen source. Induction of the production culture is performed when the production culture exhibits an OD(600) of 5-20 or 10-15. In (M2), the starting load material comprises the recombinant SAg solubilized from an ammonium sulfate precipitation of the recombinant SAg obtained from a recombinant cell lysate. The contaminants comprise bacterial endotoxin, DNA or lipopolysaccharide. The recombinant SAg following cation exchange is subjected to a second buffer exchange and cation chromatography. The recombinant cell lysate is a lysate of recombinant Escherichia coli cells containing an expression construct comprising a recombinant bacterial SAg gene operably linked to one or more expression control elements to direct expression of the recombinant SAg protein upon induction. The HIC substrate comprises a propyl, butyl, octyl or phenyl functional group, or a low or high substitution phenyl functional group. The HIC resin comprises depyrogenated phenyl-sepharose. The cation exchange chromatography separating step follows the HIC step and comprises contacting a mixture comprising a SAg and a contaminant with a cation exchange chromatography resin under conditions in which the recombinant SAg binds to the resin, and eluting the recombinant SAg from the resin under conditions in which the SAg separates from the contaminants. The substantially purified recombinant SAg comprises at least 90% recombinant SAg, and the recombinant staphylococcal *enterotoxin"** *B"** comprises at least 90% rSEB. The substantially purified recombinant SAg is essentially free of one or more contaminants comprising bacterial endotoxin, DNA or lipopolysaccharide. ACTIVITY - *Antiarthritis"** ; Immunosuppressive; Antibacterial. The potency of recombinant *staphylococcal"** *enterotoxin"** *B"** (rSEB) was evaluated in a mouse protection assay. Pathogen-free BALB/c mice 10-12 weeks old were obtained from Harlan Sprague- Dawley. Mice were maintained under pathogen-free conditions and fed laboratory chow and water and libitum. Lipopolysaccharide (LPS) from E. coli O55:B5 was obtained and reconstituted with phosphate buffered saline (PBS). Recombinant *SEB"** vaccine was diluted in 0.9% NaCl/50 mM glycine pH

8.5. Mice in groups of 10 were vaccinated intramuscularly with 5 or 20 micrograms of recombinant *SEB"** vaccine in 100 microliters of ALHYDROGEL (RTM) adjuvant or the adjuvant alone and boosted at 21 days in the same manner as described for the primary injection. Ten days after the booster vaccination, mice were challenged intraperitoneally with 10 LD50 of wild type *SEB"** and LPS (75 micrograms). Three days after challenge, the mice were scored for survivors. When immunized with 5 micrograms of rSEB, 70% of the mice challenged with wild-type *SEB"** were protected. 100% of mice were protected when challenged with wild-type *SEB"** following immunization with 20 micrograms of the recombinant vaccine protein.MECHANISM OF ACTION - Vaccine. USE - (M1) is useful for high yield production of a recombinant SAg, preferably a recombinant *staphylococcal"** *enterotoxin"** *B"** (rSEB) which is modified by amino acid substitutions at position 89 (from tyrosine to alanine), position 45 (from leucine to arginine), and position 94 (tyrosine to alanine). (M2) is useful for high yield purification of substantially purified recombinant SAg (claimed). The recombinant SAg is useful for treating disease and other conditions caused by bacterial SAgs, including food poisoning, bacterial arthritis and other autoimmune disorders, toxic shock syndrome, and insults attributed to the potential use of SAg biowarfare agents. The final rSEB product is immunogenic and protective against lethal aerosol challenge in a murine model predictive of immunogenic activity in other mammalian subjects, including human and non-human primates. rSAg is useful as an immunogen or vaccine agent, in particular as a biodefense vaccine, or for the treatment of sepsis or toxic shock. ADMINISTRATION - SAg formulation is administered at a dose of 0.01 microg/kg-10 mg/kg, preferably 0.1-0.3 microg/kg. No administration routes given. ADVANTAGE - (M1) produces high yield of rSAg. The final product of the purification process is a highly purified rSAg composition satisfying clinical safety criteria and is highly immunogenic. The rSAgs produced by the methods are safe and the purity of the rSAg in the composition is greater than 99.5%. EXAMPLE - Site-specific mutagenesis was performed using gene templates isolated from a clinical isolated of a *Staphylococcus"** aureus strain (14458) that expressed *SEB"** (sequence derivation of GenBank accession M11118). The gene was originally inserted into pBluescript II KS(+) by a PCR-based cloning strategy. Helper M13-phage were used to rescue single- stranded DNA template that was propagated in a dut,/ung mutant strain of Escherichia coli (CJ236). Modified T7 polymerase was used to synthesized second-strand DNA from synthetic oligonucleotides harboring the altered codon and single-stranded, uracil-enriched M13 templates. Mutagenized sequences were confirmed by DNA sequencing using synthetic primers, derived from known sequences or universal primers. Replicative form, double-strand DNA was isolated form E. coli host cell and the insert was shuttled to pSE380, for initial expression studies, and finally to pET24b for scale- up production by first introducing a NdeI site into the 5' end of the gene by PCR. An original seed stock of E. coli containing the recombinant *staphylococcal"** *enterotoxin"** *B"** (rSEB) gene (899445C) on plasmid pET 24b was used to prepared a master cell bank (MCB). The build up of seed stock was conducted in two stages. In the first stage, three 500 ml, triple-baffled, shake flasks were batched with 100 ml of sterile seed medium (24 g/L yeast extract, 12 g/L soytone, 4 g/L glycerol, 2.31 g/L KH2PO4, 12.5 g/L K2HPO4, and 50 microg/mL kanamycin). Each first-stage seed flask was inoculated aseptically with 1 ml (1% v/v) of pooled material from four thawed vials of the MCB. First-stage seed flasks were placed on a rotary shaker at 250 rpm and incubated at 37 degreesC. One of the flasks was selected to obtain time-course samples at one- hour intervals. The

time-course samples were processed. In the second stage, three 2000-ml, tripled baffled, shake flasks were batched with 480 ml of the sterile seed medium formulation described above. One of the flasks was selected to obtain time- course samples at one-hour intervals. The time-course samples were processed. The production stage was conducted in an 80 L fermenter with a working volume of 48 L. The production fermenter was batched with a medium comprising the same composition of the seed medium and additionally comprising 0.1% v/v of P2000 antifoam. The culture was aseptically fed 2.4 L of a sterile 10 x nutrient feed (24 g/L yeast extract, 12 g/L soytone, 4 g/L glycerol, 9.6 L purified water) at a rate of 50 mL/minute when the OD(600) reached 8+/-2, or the amount of glutamate in the production culture was less than 50% of the original glutamate concentration at inoculation. This 10 x nutrient feed was continued as long as the DO levels were greater than 20%. The culture was induced with filter-sterilized, dioxane-free isopropyl-B-D-thiogalactopyranoside (IPTG) at a 1 mM final concentration when the OD(600) reached 12.5+/-2.5. Immediately after IPTG induction, the culture was fed with 2.4 L of a filter- sterilized 20 x yeast nitrogen base solution. The culture was prepared for harvest 4 hours after IPTG induction. The recombinant *SEB"** purified was subjected to further purification. (66 pages)

4/3,AB/25 (Item 2 from file: 357)
DIALOG(R)File 357:Derwent Biotech Res.

0307431 DBR Accession No.: 2003-09216 PATENT
New nucleic acid that binds to *staphylococcal"** *enterotoxin"** *B"**, useful for treating and diagnosing e.g. septic shock, identified by the SELEX method - toxin protein production and DNA amplification for use in disease gene therapy
AUTHOR: LEVA S; KLUSSMANN S; PURSCHKE W; WIENTGES J
PATENT ASSIGNEE: NOXXON PHARMA AG 2002
PATENT NUMBER: DE 10122847 PATENT DATE: 20021121 WPI ACCESSION NO.: 2003-176796 (200318)
PRIORITY APPLIC. NO.: DE 1022847 APPLIC. DATE: 20010511
NATIONAL APPLIC. NO.: DE 1022847 APPLIC. DATE: 20010511
LANGUAGE: DE
ABSTRACT: DERWENT ABSTRACT: NOVELTY - Nucleic acid (I) that binds to *enterotoxin"** *B"** (Eb) of *Staphylococcus"**, especially S. aureus, is new. DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following: (1) preparing and/or identifying nucleic acids (Ia), particularly (I), that bind to an Eb-derived target molecule; (2) preparing L-nucleic acid (Ib) that binds to an Eb-derived target having the natural configuration; (3) complexes of Eb, especially from S. aureus, and (I); and (4) kit for detecting Eb, especially from S. aureus, that comprises (I). BIOTECHNOLOGY - Preferred Nucleic Acid: This binds to the Eb-derived sequence (Tyr)3-Gln-Cys-Tyr-Phe-Ser-Lys-Ly s-Thr-Asn-Ile-Asn-Ser-His-Gln-Thr-Asp-Lys- Arg-Lys-Thr-Cys (83) It is particularly an L-nucleic acid, RNA or DNA, and has binding constant not over 1 micro-M, particularly 250 nM or less. The specification lists 82 sequences, many of them degenerate, for (I), e.g. GGCATTGGCNYAGGWYGGTCT (Y = T, C or absent; W = A or T). Preferred Process: In method (1), a heterogeneous population of nucleic acid is prepared and contacted with an amino acid sequence from Eb. Nucleic acids that do not interact are removed; optionally those that have bound are separated and sequenced. The target is (83), a fragment of Eb

containing at least 5, particularly 15, consecutive amino acids, or a mixture of many fragments of them, with partly overlapping sequences. The selected nucleic acid may be amplified and the selection procedure repeated. In method (2), a heterogeneous population of D-nucleic acids is incubated with the optical antipode of the target sequences (as used in method (1)). Nucleic acids that interact are sequenced and the corresponding nucleic acid sequences are synthesized. ACTIVITY - Antibacterial; Immunosuppressive; Antirheumatic; *Antiarthritic"**; Dermatological. No biological data is given. MECHANISM OF ACTION - Gene therapy. USE - (I) are used to *treat"** diseases associated with Eb, specifically septic shock, rheumatoid *arthritis"** and neurodermatitis, to detect Eb (claimed) and as ligand for preparing an affinity matrix, for extracorporeal treatment of blood to remove Eb in cases of septic shock. ADMINISTRATION - (I) are administered topically or systemically. No dosage is given. ADVANTAGE - (I) have high affinity and specificity for Eb, and when they are L-nucleic acids, excellent resistance to nucleases, in vivo. EXAMPLE - The fragment (83) of *staphylococcal"** *enterotoxin"** *B"** (Tyr)3-Gln-Cys-Tyr-Phe-Ser-Lys -Lys-Thr-Asn-Ile-Asn-Ser-His-Gln-Thr-Asp-Lys- Arg-Lys-Thr-Cys (83) was biotinylated, immobilized in neutravidin-agarose and incubated with a library of nucleic acids that comprised a central randomized region of 60 nucleotides (nt), and constant flanking regions, labeled with 32-phosphorus. Bound DNAs were eluted, amplified and the selection procedure repeated, for a total of 12 rounds. The finally selected DNAs were sequenced to identify three families: (1) 7 clones with the highly conserved motif GGCATTGGCNYAGGWYGGTCT (Y = T, C or absent; W = A or T); (2) 17 clones containing the conserved motif GACATGTTAT and (3) 15 aptamers having no similarly with each other nor with (1) and (2).(52 pages)

4/3,AB/26 (Item 3 from file: 357)
DIALOG(R)File 357:Derwent Biotech Res.

0243041 DBR Accession No.: 1999-13806 PATENT
Treatment of immune disorders using a modified form of *Staphylococcus"** *enterotoxin"** *B"** which does not induce T-cell proliferation - Staphylococcus aureus *enterotoxin"**-*B"** protein engineering, used in disease therapy
AUTHOR: Sasaki T; Kimachi K; Soejima K; Kimura Y; Nozaki C; Fujiyama Y
CORPORATE SOURCE: Kumamoto, Japan.
PATENT ASSIGNEE: Chemo-Sero-Ther.Res.Inst.Kumamoto 1999
PATENT NUMBER: WO 9940935 PATENT DATE: 19990819 WPI ACCESSION NO.: 1999-508580 (1942)
PRIORITY APPLIC. NO.: JP 9850137 APPLIC. DATE: 19980215
NATIONAL APPLIC. NO.: WO 99JP638 APPLIC. DATE: 19990215
LANGUAGE: Japanese
ABSTRACT: A composition used in prevention and therapy of immune disorders is claimed. It contains a modified Staphylococcus aureus *enterotoxin"**-*B"** as the active component. The enterotoxin is modified by one or more amino acid substitutions, resulting in inhibition of its ability to induce T-lymphocyte proliferation by interaction with the V-beta component of the T-lymphocyte receptor, without causing the elimination of T-lymphocytes with the specific V-beta component of the T-lymphocyte receptor induced by natural *enterotoxin"**-*B"**. This can be used in *therapy"** of chronic rheumatoid *arthritis"** and ulcerative colitis. The enterotoxin is

preferably modified by substitution of aspartic acid at residue 9 with asparagine, asparagine at position 23 with tyrosine, isoleucine, lysine or aspartic acid or phenylalanine at position 44 with serine. Alternatively the modification may involve substitution of isoleucine at position 41 with arginine or threonine, and phenylalanine at position 44 with valine or leucine at position 45 with valine. (39pp)

- Author(s)

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Set     Items   Description
S5      11650   AU=(TAKUMI, S? OR TAKUMI S? OR SASAKI, T? OR SASAKI T?)
S6         47   AU=(KAZUHIKO, K? OR KAZUHIKO K? OR KIMACHI, K? OR KIMACHI -
              K?)
S7        427   AU=(KENJI, S? OR KENJI S? OR SOEJIMA, K? OR SOEJIMA K?)
S8       6298   AU=(YUMI, K? OR YUMI K? OR KIMURA, Y? OR KIMURA Y?)
S9        188   AU=(CHIKATERU, N? OR CHIKATERU N? OR NOZAKI, C? OR NOZAKI -
              C?)
S10       479   AU=(YOSHIHIDE, F? OR YOSHIHIDE F? OR FUJIYAMA Y? OR FUJIYA-
              MA, Y?)
S11         2   S5 AND S6 AND S7 AND S8 AND S9 AND S10
S12       114   S5 AND (S6 OR S7 OR S8 OR S9 OR S10)
S13         2   S6 AND (S7 OR S8 OR S9 OR S10)
S14        15   S7 AND (S8 OR S9 OR S10)
S15         9   S8 AND (S9 OR S10)
S16         2   S9 AND S10
S17         5   (S12 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10) AND S2
S18        23   (S11 OR S13 OR S14 OR S15 OR S16 OR S17) NOT S3
S19         9   RD (unique items)
>>>No matching display code(s) found in file(s): 65, 113

 19/3,AB/1     (Item 1 from file: 440)
DIALOG(R)File 440:Current Contents Search(R)
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13143599  References: 20
TITLE: A novel human metalloprotease synthesized in the liver and secreted
    into the blood: Possibly, the von Willebrand factor-cleaving protease?
AUTHOR(S): *Soejima K (REPRINT)"**; Mimura N; Hirashima M; Maeda H;
  Hamamoto T; Nakagaki T; *Nozaki C"**
AUTHOR(S) E-MAIL: soejima@kaketsuken.or.jp
CORPORATE SOURCE: Chemo Sero Therapeut Res Inst, Res Dept 1, /Kumamoto
  8691298//Japan/ (REPRINT); Chemo Sero Therapeut Res Inst, Res Dept 1,
  /Kumamoto 8691298//Japan/; Chemo Sero Therapeut Res Inst, Blood Prod Res
  Dept, /Kumamoto 8691298//Japan/
PUBLICATION TYPE: JOURNAL
PUBLICATION: JOURNAL OF BIOCHEMISTRY, 2001, V130, N4 (OCT), P475-480
GENUINE ARTICLE#: 481NP
PUBLISHER: JAPANESE BIOCHEMICAL SOC, ISHIKAWA BLDG-3F, 25-16 HONGO-5-CHOME,
  BUNKYO-KU, TOKYO, 113, JAPAN
ISSN: 0021-924X
LANGUAGE: English   DOCUMENT TYPE: ARTICLE
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ABSTRACT: We identified a novel metalloprotease, which could be responsible for cleaving the Tyr842-Met843 peptide bond of von Willebrand factor (vWF). This metalloprotease was purified from Cohn Fraction-I precipitate of human pooled plasma by the combination of get filtration, DEAE chromatography, and preparative polyacrylamide gel electrophoresis in the presence of SDS. The NH2-terminal amino acid sequence of the isolated protein was: AAGGILHLELLVAVGPDVFQAHQEDTRRY. Based on this sequence, we searched human genomic and EST databases, and identified compatible nucleotide sequences.

These results suggested that this protein is a novel metalloprotease, a member of the family of a disintegrin and metalloprotease with thrombospondin type-1 motifs (ADAMTS), and its genomic DNA was mapped to human chromosome 9q34. Multiple human tissue northern blotting analysis indicated that the mRNA encoding this protease spanned approximately 5 kilobases and was uniquely expressed in the liver. Furthermore, we determined the cDNA sequence encoding this protease, and found that this protease was comprised of a signal peptide, a proregion followed by the putative furin cleavage site, a reprolysin-type zinc-metalloprotease domain, a disintegrin-like domain, a thrombospondin type-1 (TSP1) motif, a cysteine-rich region, a spacer domain, and COOH-terminal TSP1 motif repeats.

19/3,AB/2 (Item 2 from file: 440)
DIALOG(R)File 440:Current Contents Search(R)

12933555 References: 38
TITLE: An efficient refolding method for the preparation of recombinant human prethrombin-2 and characterization of the recombinant-derived alpha-thrombin
AUTHOR(S): *Soejima K (REPRINT)"**; Mimura N; Yonemura H; Nakatake H; Imamura T; *Nozaki C"**
AUTHOR(S) E-MAIL: soejima@kaketsuken.or.jp
CORPORATE SOURCE: Chemoserotherapeut Res Inst, Res Dept 1, /Kumamoto 8691298//Japan/ (REPRINT); Chemoserotherapeut Res Inst, Res Dept 1, /Kumamoto 8691298//Japan/
PUBLICATION TYPE: JOURNAL
PUBLICATION: JOURNAL OF BIOCHEMISTRY, 2001, V130, N2 (AUG), P269-277
GENUINE ARTICLE#: 459MQ
PUBLISHER: JAPANESE BIOCHEMICAL SOC, ISHIKAWA BLDG-3F, 25-16 HONGO-5-CHOME, BUNKYO-KU, TOKYO, 113, JAPAN
ISSN: 0021-924X
LANGUAGE: English DOCUMENT TYPE: ARTICLE

ABSTRACT: Human recombinant prethrombin-2 was produced in Escherichia coli. The expressed prethrombin-2 formed intracellular inclusion bodies from which the protein was refolded by a simple one-step dilution process in buffer consisting of 50 mM Tris-HCl, containing 20 mM CaCl2 500 mM NaCl, 1 mM EDTA, 600 mM arginine, 1 mM cysteine, 0.1 mM cystine, 10% (v/v) glycerol, and 0.2% (w/v) Brij-58 at pH 8.5. After refolding, prethrombin-2 was purified by hirudin-based COOH-terminal peptide affinity chromatography, and then activated with Echis carinatus snake venom prothrombin activator (ecarin). The activated protein, alpha -thrombin, was then tested for several activities including activity toward chromogenic substrate, release of fibrinopeptide A from fibrinogen, activation of protein C, and thrombin-activatable fibrinolysis inhibitor, reactivity with antithrombin, clotting activity, and platelet aggregation. The kinetic data showed no differences in activity between our recombinant alpha -thrombin and plasma-derived alpha -thrombin. The yield of refolded recombinant human prethrombin-2 was about 4-7% of the starting amount of solubilized protein. In addition, the final yield of purified refolded protein was 0.5-1%, and about 1 mg of recombinant prethrombin-2 could be isolated from 1 liter of E. coli cell culture.

19/3,AB/3 (Item 3 from file: 440)

DIALOG(R)File 440:Current Contents Search(R)

08803588 References: 50
TITLE: Staphylococcal *enterotoxin"** *B"** induces *arthritis"** in female DBA/1 mice but fails to induce activation of type II collagen-reactive lymphocytes
AUTHOR(S): Omata S (REPRINT); *Sasaki T"**; Kakimoto K; Yamashita U
CORPORATE SOURCE: UNIV OCCUPAT & ENVIRONM HLTH,SCH MED, DEPT IMMUNOL/KITAKYUSHU/FUKUOKA 807/JAPAN/ (REPRINT); KIKUCHI RES CTR,CHEMOSEROTHERAPEUT RES INST/KUMAMOTO//JAPAN/
PUBLICATION TYPE: JOURNAL
PUBLICATION: CELLULAR IMMUNOLOGY, 1997, V179, N2 (AUG 1), P138-145
GENUINE ARTICLE#: XV908
PUBLISHER: ACADEMIC PRESS INC JNL-COMP SUBSCRIPTIONS, 525 B ST, STE 1900, SAN DIEGO, CA 92101-4495
ISSN: 0008-8749
LANGUAGE: English DOCUMENT TYPE: ARTICLE

ABSTRACT: It has been proposed that superantigens are involved in the pathogenesis of autoimmune diseases. To test the possibility of superantigens inducing *arthritis"** in naive mice, V beta(8)-reactive superantigen staphylococcal *enterotoxin"** *B"** (*SEB"**) was injected into naive mice. We used female DBA/1 mice, because they were susceptible to collagen-induced *arthritis"** (CIA), in which the pathogenic T cells were supposed to preferentially use limited V(beta)s of T cell receptors including V(beta)8. Mild monoarthritis developed in uninjected hindlimbs of mice administered with *SEB"** in higher frequency (an average incidence of 24%) than the control phosphate-buffered saline-injected mice (4.2%). Autoimmune responses in mice administered with *SEB"** were compared with those in mice developing CIA. However, activation of type II collagen (IIC)-reactive T cells was not detected in *SEB"**-injected mice. Production of auto-antibodies, anti-IIC antibody and rheumatoid factor was also undetected. Although exact mechanisms of pathogenesis of this *arthritis"** remain to be known, V(beta)8(+) T cells were activated for a long period and the unresponsiveness of V(beta)8(+) T cells was not detected in this strain. From these results, we discuss the pathogenesis of *arthritis"** induced by *SEB"** and the possibility that superantigen may play a role in the induction of autoimmune diseases. (C) 1997 Academic Press.

19/3,AB/4 (Item 1 from file: 348)
DIALOG(R)File 348:EUROPEAN PATENTS

01553468
GENETICALLY MODIFIED ECARIN AND PROCESS FOR PRODUCING THE SAME
ECARINE GENETIQUEMENT MODIFIEE ET PROCEDE D'ELABORATION
PATENT ASSIGNEE:
Juridical Foundation, The Chemo-Sero-Therapeutic Research Institute, (283933), 6-1, Okubo 1-chome, Kumamoto-shi, Kumamoto 860-8568, (JP), (Applicant designated States: all)
INVENTOR:
YONEMURA, Hiroshi, 1314-1, Yonnonishioki, Kawabe, Kyokushimura, Kikuchi-gun, Kumamoto 869-1298, (JP)
IMAMURA, Takayuki, 1314-1, Yonnonishioki, Kawabe, Kyokushimura, Kikuchi-gun, Kumamoto 869-1298, (JP)

NAKATAKE, Hiroshi, 1314-1, Yonnonishiki, Kawabe, Kyokushimura, Kikuchi-gun, Kumamoto 869-1298, (JP)
*SOEJIMA, Kenji"**, 1314-1, Yonnonishioki, Kawabe, Kyokushimura, Kikuchi-gun, Kumamoto 869-1298, (JP)
*NOZAKI, Chikateru"**, 1314-1, Yonnonishioki, Kawabe, Kyokushimura, Kikuchi-gun, Kumamoto 869-1298, (JP
PATENT (CC, No, Kind, Date): WO 2003004647 030116
APPLICATION (CC, No, Date): EP 2002745822 020704; WO 2002JP6770 020704
PRIORITY (CC, No, Date): JP 2001206918 010706
DESIGNATED STATES: AT; BE; BG; CH; CY; CZ; DE; DK; EE; ES; FI; FR; GB; GR; IE; IT; LI; LU; MC; NL; PT
EXTENDED DESIGNATED STATES: AL; LT; LV; MK; RO; SI
INTERNATIONAL PATENT CLASS: C12N-015/12; C07K-014/435; C12P-021/02
LANGUAGE (Publication,Procedural,Application): English; English; Japanese

19/3,AB/5 (Item 2 from file: 348)
DIALOG(R)File 348:EUROPEAN PATENTS

01553247
PROCESS FOR PRODUCING HUMAN THROMBIN BY GENE MODIFICATION TECHNIQUE
PROCEDE RELATIF A L'ELABORATION DE THROMBINE HUMAINE PAR MODIFICATION GENIQUE
PATENT ASSIGNEE:
Juridical Foundation, The Chemo-Sero-Therapeutic Research Institute, (283933), 6-1, Okubo 1-chome, Kumamoto-shi, Kumamoto 860-8568, (JP), (Applicant designated States: all)
INVENTOR:
YONEMURA, Hiroshi, 1314-1, Yonnonishioki, Kawabe, (JP)
IMAMURA, Takayuki, 1314-1, Yonnonishioki, Kawabe, (JP)
NAKATAKE, Hiroshi, 1314-1, Yonnonishioki, Kawabe, (JP)
*SOEJIMA, Kenji"**, 1314-1, Yonnonishioki, Kawabe, (JP)
*NOZAKI, Chikateru"**, 1314-1, Yonnonishioki, Kawabe, (JP
PATENT (CC, No, Kind, Date): WO 2003004641 030116
APPLICATION (CC, No, Date): EP 2002743820 020704; WO 2002JP6771 020704
PRIORITY (CC, No, Date): JP 2001206919 010706
DESIGNATED STATES: AT; BE; BG; CH; CY; CZ; DE; DK; EE; ES; FI; FR; GB; GR; IE; IT; LI; LU; MC; NL; PT
EXTENDED DESIGNATED STATES: AL; LT; LV; MK; RO; SI
INTERNATIONAL PATENT CLASS: C12N-015/09; C12P-021/02
LANGUAGE (Publication,Procedural,Application): English; English; Japanese

19/3,AB/6 (Item 3 from file: 348)
DIALOG(R)File 348:EUROPEAN PATENTS

01522449
VON WILLEBRAND FACTOR (VWF)-CLEAVING ENZYME
ENZYME DE CLIVAGE DU FACTEUR DE VON WILLEBRAND (VWF)
PATENT ASSIGNEE:
Juridical Foundation, The Chemo-Sero-Therapeutic Research Institute, (283933), 6-1, Okubo 1-chome, Kumamoto-shi, Kumamoto 860-8568, (JP), (Applicant designated States: all)
INVENTOR:

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DESIGNATED STATES: AT; BE; CH; CY; DE; DK; ES; FI; FR; GB; GR; IE; IT; LI; LU; MC; NL; PT; SE; TR
EXTENDED DESIGNATED STATES: AL; LT; LV; MK; RO; SI
INTERNATIONAL PATENT CLASS: C12N-015/57
LANGUAGE (Publication,Procedural,Application): English; English; Japanese

19/3,AB/7 (Item 1 from file: 357)
DIALOG(R)File 357:Derwent Biotech Res.

0309279 DBR Accession No.: 2003-11064 PATENT
New genetically-modified ecarin for mediating the cleavage of prethrombin-2 to give alpha-thrombin, or for mediating the conversion of mesothrombin from prothrombin, for use in medicines e.g. hemostatics - recombinant ecarin production for use in hemostatic therapy
AUTHOR: YONEMURA H; IMAMURA T; NAKATAKE H; *SOEJIMA K"**; *NOZAKI C"**
PATENT ASSIGNEE: CHEMO-SERO-THERAPEUTIC RES INST 2003
PATENT NUMBER: WO 2003004647 PATENT DATE: 20030116 WPI ACCESSION NO.: 2003-210365 (200320)
PRIORITY APPLIC. NO.: JP 2001206918 APPLIC. DATE: 20010706
NATIONAL APPLIC. NO.: WO 2002JP6770 APPLIC. DATE: 20020704
LANGUAGE: Japanese
ABSTRACT: DERWENT ABSTRACT: NOVELTY - A genetically-modified ecarin for mediating the cleavage of prethrombin-2 at the Arg-Ile site to give alpha-thrombin, or for mediating the conversion of mesothrombin from prothrombin, is new. DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for producing a recombinant ecarin comprising: (a) culturing a transformant constructed by transforming a microbial or animal cell with an expression vector carrying a gene that encodes ecarin integrated downstream of a promoter, and collecting the produced and accumulated ecarin in the culture medium or transformant; and(b) recovery the ecarin for purification. BIOTECHNOLOGY - Preferred Ecarins: The recombinant ecarin has an amino acid sequence (I) of 616 amino acids or its partial sequence, or any peptide based on the sequence of (I) or its partial sequence but with some amino acids deleted, substituted or added. Preferred Process: The promoter is a simian virus (SV)40 initial-stage promoter, a SV40 later-stage promoter, a cytomegalovirus promoter or a fowl beta-actin promoter, especially a fowl beta-actin promoter. The expression vector has a signal sequence at the upstream of a gene encoding ecarin. The signal sequence a pelB signal, an alpha factor signal, a signal SG-1 of immunoglobulin and a signal of C25. The expression vector may also have a gene-amplifying gene, and culturing of the transformant is subsequently carried out under gene-amplifying conditions. This

gene-amplifying gene is particularly the dihydrofolate reductase-encoded gene. The ecarin-encoded gene is a gene fragment with a base sequence of (II) of 1863 base pairs, or a gene fragment encoding a peptide that encodes an amino acid sequence of a part of the ecarin protein. The transformant is preferably an animal cell chosen from a Chinese hamster ovary cell (CHO cell), a mouse myeloma cell, a baby hamster kidney (BHK) 21 cell, a 293 cell and simian fibroblast (COS) cell. ACTIVITY - Hemostatic. MECHANISM OF ACTION - Endopeptidase. USE - A new method is used for the production of genetically-modified ecarin for specific activation of prethrombin into thrombin (claimed), for use in medicines e.g. hemostatics. ADVANTAGE - By applying this method, ecarin can be produced on an industrial scale. EXAMPLE - An expression plasmid pCAGG-S1 (Sal) was constructed, followed by pCAGG-S1 (Sal).dhfr (dihydrofolate reductase), pCAGG-S1(Sal).dhfr.neo and pCAGG-S1(Sal).mdh fr, as well as the snake ecarin expression plasmid pCAGG-S1.ECdhfr.neo. Chinese Hamster Ovary (CHO) DG44 cells were transferred with the plasmid for producing a recombinant ecarin. (31 pages)

19/3,AB/8 (Item 2 from file: 357)
DIALOG(R)File 357:Derwent Biotech Res.

0309277 DBR Accession No.: 2003-11062 PATENT
Production of human thrombin by genetic modification, for use in drugs e.g. as hemostatics - recombinant protease enzyme production useful for drug screening and disease therapy
AUTHOR: YONEMURA H; IMAMURA T; NAKATAKE H; *SOEJIMA K"**; *NOZAKI C"**
PATENT ASSIGNEE: CHEMO-SERO-THERAPEUTIC RES INST 2003
PATENT NUMBER: WO 2003004641 PATENT DATE: 20030116 WPI ACCESSION NO.: 2003-210361 (200320)
PRIORITY APPLIC. NO.: JP 2001206919 APPLIC. DATE: 20010706
NATIONAL APPLIC. NO.: WO 2002JP6771 APPLIC. DATE: 20020704
LANGUAGE: Japanese
ABSTRACT: DERWENT ABSTRACT: NOVELTY - Producing human thrombin using a gene modification technique comprising culturing a transformant, conversion of the recovered human prethrombin into human thrombin after activation by treatment with ecarin, and purifying human thrombin from the reaction mixture, is new. DETAILED DESCRIPTION - Producing human thrombin with use of a gene modification technique comprises: (a) culturing a transformant constructed by transforming an animal cell with an expression vector carrying a gene that encodes prethrombin integrated into the downstream of a promoter and accumulating the thus produced prethrombin in the cell culture medium for collection; (b) conversion of the recovered human prethrombin into human thrombin after activation by treatment with ecarin; and (c) purifying such human thrombin from the reaction mixture. BIOTECHNOLOGY - Preferred Method: The promoter is selected from SV40 initial-stage promoter, SV40 later-stage promoter, cytomegalovirus promoter and fowl beta-actin promoter, especially fowl beta-actin promoter. The expression vector has a signal sequence at the upstream of a gene encoding prethrombin. Such signal sequence is selected from pelB signal, alpha factor signal, signal SG-1 of immunoglobulin and signal of C25. Such expression vector may also have a gene-amplifying gene, and cultering of the transformant is subsequently carried out under gene-amplifying conditions. This gene-amplifying gene is particularly the dihydrofolate reductase-encoded gene, e.g. a gene fragment with a base sequence of (XI) with 1072 base pairs. The transformant is preferably an animal

cell chosen from a Chinese hamster ovary cell (CHO) cell, mouse myeloma cell, BHK 21 cell, 293 cell and COS (a cell line derived from the african green monkey cell). Activation of prethrombin uses an ecarin produced by the gene modification technique. ACTIVITY - Hemostatic. No biological data given. MECHANISM OF ACTION - None given. USE - The method is useful for the production of human thrombin by genetic modification, which can be used in drugs e.g. as hemostatics. ADVANTAGE - Using the inventive method, human thrombin can be produced in large quantities at high safety and low cost while minimizing effects of the blood-originated components. EXAMPLE - An expression plasmid pCAGG-S1 (Sal) was constructed, followed by pCAGG-S1 (Sal).dhfr, pCAGG-S1(Sal).dhfr.neo and pCAGG-S1(Sal).mdhfr, as well as the human prethrombin-2 expression plasmid. CHO DG44 cell were transferred with the plasmid for producing prethrombin (90 mug/ml obtained) which was activated to give human thrombin for purification. (38 pages)

19/3,AB/9 (Item 3 from file: 357)
DIALOG(R)File 357:Derwent Biotech Res.

0306788 DBR Accession No.: 2003-08573 PATENT
von Willebrand factor-cleaving enzyme, applicable in diagnosis of, and supplementary therapy for, thrombotic thrombocytopenic purpura, and for developing drugs for e.g. myocardial infarction and cerebral infarction - recombinant protein production and antagonist and agonist for use in gene therapy
AUTHOR: *SOEJIMA K"**; MIMURA N; MAEDA H; *NOZAKI C"**; HAMAMOTO T; NAKAGAKI T
PATENT ASSIGNEE: CHEMO-SERO-THERAPEUTIC RES INST 2002
PATENT NUMBER: WO 200288366 PATENT DATE: 20021107 WPI ACCESSION NO.: 2003-120479 (200311)
PRIORITY APPLIC. NO.: JP 200217596 APPLIC. DATE: 20020125
NATIONAL APPLIC. NO.: WO 2002JP4141 APPLIC. DATE: 20020425
LANGUAGE: Japanese
ABSTRACT: DERWENT ABSTRACT: NOVELTY - A protein-decomposing enzyme (protease) capable of cleaving the 842Ty-843Met bond of von Willebrand factor (vWF) comprises a partial sequence of a polypeptide chain Leu-Leu-Val-Ala-Ala-Val or its variant derived by deletion, substitution or addition of some amino acids in the amino acid sequence of such polypeptide chain. DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for: (1) A gene fragment encoding the protease; (2) A DNA encoding a protein with a base sequence that encodes a polypeptide with an activity of cleaving the 842Ty-843Met bond of vWF and containing a base sequence of CTGCTGGTGGCCGTG, or its variant with some bases deleted, substituted or deleted from the sequence; (3) A vector containing any of the DNAs; (4) Cells, or host cells, transformed or transfected by the vector; (5) Drug compositions containing the protease; (6) An antibody against any of the proteases; (7) Purifying the protease by using the antibody; (8) Drug compositions or diagnostics containing the antibody; (9) Antagonists, inhibitors, agonists or activity regulators of the protease; (10) Drug compositions or diagnostics containing these antagonists, inhibitors, agonists or activity regulators of the protease; (11) Assay of vWF-cleavage activity by recovering a substrate sample by filtering after the reaction of vWF and vWF-cleaving enzyme on a membrane filter for enzyme-substrate reaction before analysis by SDS-PAGE without Western blotting; (12) Screening compounds cleaving vWF by measuring

vWF-cleavage activity of the test compound by the assay method; (13) Preparing the protease by using human plasma fraction I paste as the starting material; (14) Homologs of the protease or analogous proteins in other animal species; (15) Genes encoding the homologs of the protease or analogous proteins in other animal species; and (16) Animals modified with genes encoding these homologs of the protease or analogous proteins in other animal species. BIOTECHNOLOGY - Preferred Enzymes: Such polypeptide chain particularly has a part of the N-terminal amino acid sequence of a mature protein Ala-Ala-Gly-Gly-Ile-Leu-His-Leu-Glu-Leu-Leu-Val-Ala-Val, or its derivative obtained by deletion, substitution or/and addition of some amino acids. The partial N-terminal amino acid sequence of such mature protein especially has a sequence of (III) or (VII) both with 16 amino acids, its derivative obtained by deletion, substitution or/and addition. The polypeptide chain can also be one with some amino acids deleted, substituted or added to any of the amino acid sequences of (XVI)-(XXI) of 270-1378 amino acids, which has a molecular weight from 105-160 or 160-250 kDa when determined by SDS-PAGE under reducing or non-reducing conditions. Preferred Nucleic Acids: Such DNA may contain a base sequence of GCTGCAGGCGGCATCCTA CACCTGGAGCTGCTGGTGGCCGTG or its variant, e.g. of sequence (VI) or (XV) with 483 or 4950 base pairs, respectively, or their variant. Preparation: The enzyme was prepared by standard recombinant techniques. ACTIVITY - Anticoagulant; Thrombolytic; Hemostatic; Cardiant; Cerebroprotective; Antiarterioscler otic; Hepatotropic. No biological data given. MECHANISM OF ACTION - Protease Inhibitor; Gene Therapy. USE - The enzyme and its encoded DNA are applicable in the diagnosis of, supplementary therapy for thrombotic thrombocytopenic purpura (claimed), and developing drugs for e.g. myocardial infarction, cerebral infarction, arteriosclerosis, platelet thrombosis and stenosis, including gene therapy. ADMINISTRATION - Administration is particularly by injection e.g. at 1 microg to 100 mg. ADVANTAGE - The enzyme can be produced easily with stable supply. EXAMPLE - The enzyme was prepared as follows .A plasma fraction and the vWF were obtained by filtration then fractionation on a Sepharcryl S-500HR (RTM) column. Activity of the isolated vWF was confirmed by using labeled vWF antibody and the Western blot method. Usefulness of the enzyme was checked. Its DNA and antibody were also produced for testing. (144 pages)

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